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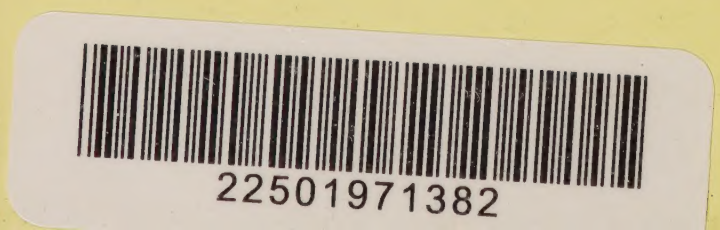

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PUBLIC HEALTH

REPORTS

OF

THE MEDICAL OFFICER OF THE PRIVY COUNCIL AND LOCAL GOVERNMENT BOARD.

NEW SERIES, No. VIII.

REPORT TO THE LORDS OF THE COUNCIL ON SCIENTIFIC INVESTIGATIONS, MADE UNDER THEIR DIRECTION, IN AID OF PATHOLOGY AND MEDICINE.

Presented to both Houses of Parliament by Command of Her Majesty.

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REPORT.

TO THE LORDS OF HER MAJESTY'S MOST HONORABLE PRIVY COUNCIL.

MY LORDS,

MEDICAL OFFICER'S REPORT

IN accordance with the desire which your Lordships, on my retirement from office, did me the honour of expressing to me, that, when the various reports which were yet to accrue from the Medico-Scientific Investigations of last financial year should be complete, I (though no longer in office) should fulfil the agreeable duty of seeing to their passage through the press, I submit the present volume to your Lordships; and as the date of my doing this is by some months later than I had hoped it would be, I beg leave to state that the completion of the printing has been delayed by circumstances not in my control.

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1. The first report which the volume contains is a further contribution by Dr. Sanderson to the study of the Morbific Ferments. It relates particularly to the common ferment of putrid infusions, —a ferment which, besides having power to excite putrefaction in dead animal matter, has (as former of these reports have shown) very definite toxical relations to the living animal body. Dr. Sanderson now shows that, if infusions which have the septic ferment in them be passed under pressure through porous porcelain, the filtrate (which after such filtration has no microphytic organisms in it) will now not undergo any further zymotic process in itself, and, if introduced into the living body, will not exercise any morbific influence on it. These results have at least an important negative bearing: for, had contrary results been obtained, and had the septic liquid been shown to contain its characteristic ferment in the mechanically-inseparable state of true solution, this fact would have conflicted with our opinion, previously expressed, that the morbific ferments are essentially particulate, and probably have their essence, or part of their essence, in the multiplying organic forms (microzymes) which they contain.*

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* As regards the component parts of the previous opinion, it will be observed that Dr. Sanderson in the present paper, though apparently still supposing that the septic ferment is particulate, seems to regard as proven by Professor Panum's experiments, as well as approximately by his own, that it "does not consist of living organisms." I think it better not to attempt on the present occasion to follow any of the lines of consideration which suggest themselves with regard to that distinction.

But while the verdict is to that extent distinctly in favour of the previous opinion, the test cannot, I apprehend, be considered unambiguous for purposes of positive argument, till we know for certain that the filtration-process, which obviously does arrest all visible particles, does not at the same time effect any other change which can be deemed essential in the liquid which goes through the filter.

This report from Dr. Sanderson represents all that his other engagements would allow him to do in the way of scientific investigations under your Lordships during the year 1875–6; and I much regret to have to state that, at the time when my own official connexion with the Department was ending, Dr. Sanderson had found himself unable to accept any commisssion under your Lordships for the year which is now drawing to its close.

2. The next three papers in the volume are by Dr. Klein. The first of them (App. No. 2) is a short memorandum in which he refers to his previous report on Sheep-Pox, and rectifies a very important error of interpretation in that report. It had chanced that Dr. Creighton, while studying preparations which he had made of glandular textures for the purpose of his own researches in Cancer, came on appearances so similar to some of those branching forms which had been found by Dr. Klein in the skin-eruption and skin-lymphatics of variolous sheep, but at the same time so certainly due to his own method of anatomical preparation, that he was led to believe that Dr. Klein's interpretation of the sheep-pox appearances had been in part erroneous; and upon his doing me the favour of drawing my attention to the supposed fallacy, which I at once brought to Dr. Klein's notice, Dr. Klein returned to his examination of the variolous specimens, and eventually came fully to recognise that Dr. Creighton's contention was just. The effect of the above correction is to set aside as mistaken those parts of Dr. Klein's paper which represent the higher fungic structures, mycelium and gonidia, as existing in variolous skin; and on consideration of all the circumstances, I am disposed to think that provisionally we ought to regard this correction as applying also to certain parts of Dr. Klein's paper on enteric fever, and as invalidating, till further examination shall have been made, the descriptions which he there gives of higher fungic forms in the follicles of the diseased intestines. Dr. Klein is confidently of opinion that the correction does not in either case affect those parts of his description which represent the diseased textures as pervaded by swarms of micrococci; and this is also the opinion of Dr. Sanderson, under whose superintendence the former researches were made; but as it will, I think, clearly be convenient that Dr. Klein should at the earliest opportunity re-write, under the present correction, his account of the morbid anatomy of the two diseases, I would suggest that, in preparing to do this, he should re-examine, so far as any doubt could be raised, the whole ground of the former investigations.

As regards the curiously fallacious microscopical forms by which Dr. Klein was misled, I think it due to him to state that not only did those forms lead other skilled animal-histologists who saw them to concur with him in believing them to be extrinsic organisms, but that also botanists of the highest European authority accepted them without demur as truly fungic.

3. Dr. Klein's next paper (App. No. 3) gives the results of an elaborate investigation he has made of the intimate anatomical changes which arise in various organs of the body during the progress of severe Scarlatina.

His results, so far as the investigations have gone, do not seem to me to justify any final opinion with respect to the nature of the scarlatinal contagium; but the detailed illustrations which he gives of the peculiar working of the infection in a great variety of organs seem to me a very interesting addition to previous knowledge, both as regards the scarlatinal infection in particular, and as regards febrile infections in general. In these points of view I would especially draw attention to the evidence which Dr. Klein seems to find that scarlatina tends to produce widely-diffused textural changes in the walls of bloodvessels,—a hyaline swelling of the texture of capillary vessels and of the inner layer of minute arteries, and also an abundant growth of new elements in the contractile layer of the arterioles: changes which (as affecting the perviousness and contractility of the vessels) may of course, in their turn, be productive or partly productive of other lesions.

I would connect Dr. Klein's observation of these changes, as incidental to scarlatina, with his previous but less elaborated observation of like changes in cases of enteric fever. Diffused bloodvessel-changes, started in that inner surface of the vessels which has immediate contact with the circulating blood, can hardly not be ascribed to the blood as their cause; and moreover, in both the diseases here referred to, grosser blood-change is occasionally attested by clots which form in the course of the circulation, and become impacted as plugs (so-called *emboli*) in the smaller vessels. The tendency to form "emboli" is known to be likewise an attribute of the septic infections; and at least in them it seems certain that the clotting-process is determined by minute masses of shaped zymotic material which act as nuclei for such concretion.

Dr. Klein has not hitherto found in scarlatina anything which he can confidently regard as a microphytic contagium; for, though he no doubt did see, in some cases, in special combination, an abundant presence of well-marked micrococci, this was only where the circumstances rather favoured a supposition that the micrococci were of secondary occurrence; and he for the present reserves his opinion with regard to the doubtful appearance of micrococci which he found in the scarlatinal skin at an early stage of the disease.

4. Dr. Klein's final paper (App. No. 4) is a summary account of some studies which he has made of a certain infective Fever of Swine. The special reason for this research was that the disease in question had been supposed to be identical with the enteric fever of the human subject; and hope was entertained that therefore our studies of the human disease might be usefully supplemented by studies of the brute. In the event this hope was not realised: for Dr. Klein's research soon showed that the two diseases differ in respects which appear to be essential, and the human disease therefore cannot for the present be studied in other than its human relations. But the research, though in that respect fruitless, has given results which in other ways are of much interest, both as contributing to veterinary practice the more exact knowledge of an important disease of live stock, and also as adding a very interesting new illustration to zymotic pathology in general. In the latter point of view I would draw particular attention to Dr. Klein's description of the state of the lungs and pleura in this pig-disease, as regards the plugging of pulmonary blood-vessels and lymph-vessels, as well as small air-tubes, with micrococci, and as regards the extraordinary diffusion of micrococci on the surface of the serous membrane.

5. In the fifth paper of the present volume (App. No. 5) Dr. Creighton reports on such further studies of Cancer as he had made down to the end of the financial year. The report is a chapter in the natural history of those ineradicable and indefinitely-advancing infective growths which in surgical practice are emphatically called "malignant;" and it particularly relates to the intimate anatomical changes which arise in lymph-glands, when cancer, operating from some spot in which it has been of primary occurrence, secondarily spreads its infection to them.

In explanation of the fact, familiar in pathology, that, in the consecutive extensions of cancer in a given affected body, the secondary and tertiary tumours tend to repeat with an exact mimicry the special pattern of the primary tumour, pathologists have had two different surmises as to the nature of the secondary and subsequent processes: one, that such acts of infection are merely of the nature of a transplantation or botanical grafting-process,—that effluent living elements of the primarily-diseased parts, passing into streams of lymph or blood, and carrying with them a strong germ-power of their own, grow indefinitely on their original plan, and as parasites, in the parts to which they are floated, and in which they chance to take root; the other, that not a mere transplantation, but a zymotic process, is signified by the extensions of cancer,—that the elements of the primarily-diseased part have in them a specific ferment-power, by which, if lymph-stream or blood-stream carries them to another part, they enforce on that part, as with a kind of impregnation, that it, deserting its own former textural type, shall grow in a new way with new endowments, so as to become in form and ferment-power a repetition

of the parent tumour. The former of these two opinions was that which, before the beginning of Dr. Creighton's researches, was, I believe, the more generally entertained in this country,* and, while nothing was shown to the contrary, might easily have been judged the more probable (because apparently the simpler) explanation of facts: but Dr. Creighton's report of 1874, on the development of secondary cancer-nodules in the liver, pointed decidedly to the other conclusion; and his present report, on the cancerisation of lymph-glands, speaks again in the same sense. He had, it is true, one class of cases in which he could identify in the diseased lymph-glands characteristic forms, derived in considerable quantity from the primarily-diseased part; and in this class of cases, taken alone, it no doubt was difficult or impossible to determine whether given tumour-forms existing in the lymph-gland were mere colonists derived (with or without multiplication) from the primary disease, or were an essentially new generation to which the gland itself, by reason of its being infected, had given rise. But the ambiguity which in such cases attached to the phenomena because of the large quantity of the foreign material was, in cases of a different class, comparatively absent. In some cases, namely, material which could be identified as coming from the primary disease was present in given lymph-glands in but so small quantity that the behaviour of the individual migrants, or of separate little groups of them, could be advantageously studied; and in the very valuable set of observations where this was done by Dr. Creighton, he saw no signs as of migrants preparing to pass by mere self-augmentation (after the manner of vegetable grafts) into the new growth which was to follow their arrival. On the contrary, in observations which appear to have been the most instructive of the series, migrants, when they had attained their fullest type of character, seemed merely to undergo dissolution in contact with the gland-soil onto which they had been cast; perhaps diffusing into it at the point of contact as the spermatozoon into the ovum which it impregnates; while, contemporaneously with this their dissolution, the contiguous portion of gland-substance straightway began to show in its individual elements that it had become subject to an alien power, under which it must pervert its own growth to those new and destructive issues which are common to cancerised organs. And Dr. Creighton's observations to that sort of effect acquire an additional importance when they are considered in conjunction with a third set of observations which he describes: cases, namely, in which the infected lymph-gland not only gave, so far as he could see, no evidence of having received shaped migration from the primary disease, but in which moreover the signs of its incipient secondary infection were diffused in it so generally and so equably as almost to exclude the thought of mere transplantation.

* See, for instance, the very interesting discussion which was held on the subject of Cancer two years ago at the Pathological Society of London, and particularly the admirable paper with which the late Mr. Campbell De Morgan then introduced the subject for debate.—*Path. Trans.*, Vol. 26.

It seems to me of great interest to pathology, in some of its most promising relations to the future improvement of practice, that researches like these which Dr. Creighton has begun should be followed to their very utmost yield; and in view of the high qualifications with which Dr. Creighton had been prosecuting these researches, I found cause for particular regret in learning from him towards the close of the year's work here reported on that I might not propose to your Lordships his further continuance in the work.

6. The last paper (App. No. 6) in the present volume is by Dr. Thudichum, continuing his former reports by a provisional account of certain further studies which he has made of the Chemical Constitution of the Brain. Though Dr. Thudichum's work in this investigation has been and is continuous, yet, having regard to its very great extent and its extraordinary difficulty, he does not anticipate that for the next two or three years he will be in a position to give his concluding report on it—a report as comprehensive as that which he submitted two years ago, and containing also his pathological applications of the study; but pending this completion of the entire scheme, there are results of each year which admit of being separately stated; and, just as last year so again now, Dr. Thudichum has presented an interim report with much highly interesting detail in it.

The report chiefly occupies itself with the intimate chemistry of certain of the complex bodies which were described in the former report as immediate principles of the brain, particularly of those of the so-called *cerebrine* (nitrogenous) series; studying, in regard of each such principle, what is its exact eventual yield of elements, and what its exact process of break-up, under artificial chemical treatment. The general importance of this kind of study, as conducing to the interpretation of the chemical changes which are effected by disease in the living body, and as indeed often an indispensable clue for such interpretation, is, I believe, now generally recognised among pathologists; and there are points in the present paper which seem to me strikingly to illustrate it. Thus, the fact, now clearly established by Dr. Thudichum, that sugar is apt to arise as one of the decomposition-products of cerebrine, is highly suggestive in relation to the familiar occurrence of so-called "amyloid bodies" in the diseased nerve-centres of persons who have suffered certain sorts of paralysis, and perhaps also (in a different way) in relation to one interesting section in the obscure ætiology of diabetes; and, in another direction, it is equally suggestive to find that the new crystalline alkaloid which Dr. Thudichum exhibits as a product of brain-destruction, appears to be of intimate affinity with certain chemical compounds which are known as contents or derivates of bile.

Finally, my Lords, adverting to the fact that my tenure of office under your Lordships did not terminate till nearly two months

after the end of the period to which the foregoing report relates, I believe it may be right for me here to state that, during these two months, no work, except such as was of the nature of continuation-work, was undertaken in this branch of your service: for your Lordships had, for parliamentary reasons, determined that you would not till late in the session move Parliament for the usual annual grant for the Scientific Investigations; and under these circumstances the programme which I had in readiness for your Lordships' consideration, with regard to work to be done in the new financial year, necessarily remained in great part in abeyance. I may perhaps be permitted to mention that, among the diseases which I was hoping this year to submit to systematic investigation (in addition to those in regard of which our previous work had to be continued or extended) the first was Rheumatic Fever; and I would also mention that our studies of the obscure problems of zymotic pathology had at so many points (as various sections of the present volume may illustrate) made us aware of the insufficiency of present knowledge of the Natural Ferments of the living animal body, that I was further hoping with your Lordships' sanction to initiate a systematic study of this very difficult physiological subject-matter.

Though now myself removed from further active participation in the medical service of the State, I must continue to feel warm interest in whatever shall promote the progress of that service; and your Lordships, graciously crediting me with this, were so good as to inform me, on my leaving office, that Government intends to continue these investigations. The connexion of them with your Lordships' Medical Department was always felt by me, while in office, as an invaluable aid, co-operative and consultative, in directions where my own working-power (under prior claim of other engagements) necessarily fell short of my wishes; and I daresay that, by my successors under the Local Government Board, the privilege of the official association with scientific research will be appreciated as highly as it was by me. As for the general value and promise of that kind of work in its bearing on the progress of Medicine, I entertain the strongest conviction that, in regard of all antagonism to disease, whether with preventive or with curative measures, and whether by official or by private hands, Medicine's best prospects of increased success are inseparable from such studies of exact science, and that, in proportion as the pathological insight becomes more clear, the growth of practical power will certainly follow. The investigations which have been made under your Lordships' authority have, I need hardly say, only pretended to deal with selected portions of the vast subject-matter of Pathology. Their distinctive aim (as explained in a former report) has but been to supplement, in particular matters and methods of research, other and ordinary agencies of medico-scientific progress: in directions, namely, where research, if it is to succeed, requires systematic and continuous labour extending over long periods of time—labour, not only inconducive to immediate pecuniary profit, but perhaps involving much cost; and

where, such being the conditions, it can hardly be expected that the study, however great its eventual importance, will be adequately cultivated by private investigators. That the investigations, instituted by your Lordships on that limited basis, have even in these few years been of very real instructiveness to the Medical Profession in this country, and that, besides such direct gain of knowledge as they have given, they have very greatly stimulated the general spirit of pathological investigation among us, will not, I believe, be questioned by anyone who knows the medico-scientific records of the time; and in view of their intended continuance, I would express to your Lordships, though now but as an individual practitioner, my thankfulness for the aid which Government will thus be giving to the culture of the Profession to which I belong.

I have the honour to be, my Lords,
Your Lordships' obedient humble servant,
John Simon.

London;
February, 1877.

APPENDIX.

No. 1.

Dr. Sanderson's Report of a further Investigation of the Properties of the Septic Ferment.

Introduction.

The experimental inquiry, of which an account is given in the following pages, was undertaken for the purpose of obtaining more precise information as to the nature and properties of the poisonous substance to which septic liquids owe their virulence.

It has been long known that the aqueous infusions of putrid animal tissues, as for example flesh, produce, when introduced into the circulating blood of the higher animals, certain characteristic febrile and other symptoms which are recognised as those of septic infection. These symptoms were first studied early in the present century by Gaspard, and subsequently by Magendie. In more recent times they have been made the subject of more precise and extended investigations by Panum,* by Otto Weber,† and finally by Bergmann and his pupils.‡

Bergmann§ was led by his researches to infer that the septic poison is a chemical body held in solution by the water of infusion, and accordingly undertook, in co-operation with his colleague Professor Schmiedeberg, researches with a view to its separation by chemical methods. The results of those inquiries are well known. A product was obtained which was believed to be a pure substance, and called *sepsin*. The most characteristic fact relating to it was that when its solution was introduced into the living organism, it produced a pyrexia of several hours' duration, of which the temperature curve corresponded so closely with that of the pyrexia produced by the injection of small doses of septic liquids, that the identity could not be mistaken. This curve has been since often referred to as the sepsin curve by pathological writers.

Twelve years before Bergmann wrote, the subject had been investigated by Professor Panum of Copenhagen; as however his researches were published only in Danish, they failed to exercise their due influence. Subsequently (in 1863), a short account of the work was published in Virchow's Archiv by the author, who further, in 1874, contributed a complete paper on the subject to the same journal. The question to which Panum's attention, particularly in his earlier researches was chiefly directed, was that of the participation of the minutest living forms in the production of the symptoms of septichæmia. "Is "it the case," he inquired, "that the microscopical organisms which "are always present in putrid liquids, stand in such relation with

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* P. L. Panum, Bibliothek for Läger, April 1856, pp. 253-285. Virchow's Archiv Bd. 27 (1863). Experimentelle Untersuchungen zur Physiologie und Pathologie der Embolie, Transfusion und Blutmenge, Berlin, 1864.—Virchow's Archiv Bd. 60 (1874).

† Otto Weber, Experimentelle Studien uber Pyæmie, Septicæmie und Fieber. Deutsche Klinik, 1864–65.

‡ Bergmann, Das putride Gift und die putride Intoxication, Dorpat, 1868.—Zur Lehre von der putriden Intoxication, Deutsche Zeitschrift für Chirurgie Bd. I., p. 376.

The researches of Bergmann's pupils are embodied in a series of academical dissertations of the University of Dorpat, printed between the years 1866 and 1869, by Weidenbaum, von Raison, Petersenn, Schmidt, and some others.

§ Bergmann und Schmiedeberg, Ueber Sepsin. Centralblatt, 1868, p. 497.

"the group of symptoms which are observed when such liquids "find their way into the circulating blood, or into the tissues, that "these symptoms cannot present themselves, if the infecting liquid "is either deprived of its organisms, or subjected to some process by "which their vitality is destroyed." This question Panum answered in the negative. Approaching the subject with a decided bias in the opposite direction, derived from the consideration of the then recent investigations of Helmholtz as to the intimate relation between the chemical process of putrefaction and the morphological changes which are associated with it, he was led, by the study of the nature and development of the symptoms themselves, to doubt whether, granting that that relation were admitted to be completely established, there was sufficient ground for applying the conceptions founded on it to the explanation of pathological actions. Thus, for example, the easily recognized fact that in septic poisoning there is no period of incubation, that the introduction of the deleterious agent into the circulation is immediately followed by the manifestations of its action, seemed altogether irreconcilable with the hypothesis that any such multiplication of virulent material as is supposed to constitute the processes of specific infection, takes place in the infected organism. At the same time he fully recognised that there might be other ways in which these living particles might act morbifically, so that the possibility of their pathogenic action could not be entirely disregarded.

These were the considerations which led Panum to undertake his investigations. It is to be remembered that at the time that he did so, the "germ theory" had not been heard of, that no one had written about "microzymes," and that bacteria were familiar only to morphologists. He had the merit, not only of recognising clearly the importance of the pathological questions which have since become associated with these now familiar expressions, but of making a most important step in their investigation. The method he adopted was excellent. Having first carefully studied the pathological process itself so as to determine its characteristics, and to be able to recognise them with certainty, and having ascertained that they were the constant results of the introduction into the circulation of certain kinds of putrid infusions, he set to work to devise a method by which the influence of the particular factor of which the potency was in question, namely the living organisms contained in such infusions, could be separately tested. With this view the following plan of experiment was adopted: An infusion of flesh having been allowed to stand in a warm room for two or three weeks, was carefully filtered, then boiled for several hours and finally evaporated to dryness on a water bath. The thoroughly dry residue was then digested first with cold and then with boiling absolute alcohol. After the alcoholic extract had been removed and set aside, the insoluble residue was extracted, first with cold then with boiling distilled water, and filtered hot. The aqueous extract, which obviously contained exclusively material insoluble in absolute alcohol, when injected into the circulation of dogs in a number of instances, produced in all, the characteristic symptoms of septic infection. The following experiment may serve as an example of the rest.

The material employed was an infusion, of which 24 cub. centims. (yielding 0·071 gramme of solid residue on evaporation) produced death in six hours when injected into the venous system of a small dog. Thirty cub. centims. of aqueous extract prepared from this liquid in the way above described (of which 10·34 grammes yield 0·004 gramme of solid residue) were injected into the jugular vein of a full-grown dog. It will be sufficient to give a short summary of the symptoms, which

are described in the original with great minuteness. About half an hour after the injection, the animal began to be unwell. About 15 minutes later there were horripilation along the back, and slight twitchings of the muscles of the extremities. Soon after retchings commenced and the ropy saliva was copiously discharged from the mouth. Then followed frequently repeated efforts to discharge fæces, the evacuations being at first natural, then accompanied with much mucus. At the end of two hours the pulse was accelerated, and the pupils were strongly dilated, and the depression was already so great that the animal was unable to stand, the alvine symptoms remaining as before. After the fourth hour the dog began to improve. The following morning it was willing to take food, and was rapidly recovering. It was then killed by pithing and immediately dissected. The only pathological appearances observed were those referable to the intestine. The mucous membrane of the duodenum exhibited tracts of congestive hyperæmia, and it was so much swollen that the patches of agminate glands appeared as insular depressions.

On these facts Panum comments as follows:—"It appears to me hardly "possible that anyone, in face of these observations can seriously believe "that here, notwithstanding the filtration, the boiling prolonged for "hours, the evaporation to dryness at the boiling temperature, the "digestion with cold and boiling absolute alcohol, the extraction with "boiling water, and the final filtering, living organisms were still present, "which were not destroyed;" and concludes, "That it may be regarded "as a completely established fact that there exists in putrid fluid a "specific chemical body which is soluble in water, and is endowed with "the property when introduced into the circulating blood, of calling "into existence that peculiar group of symptoms which are recognised "as those of septic infection . . . . retaining that power, notwith-"standing that the liquid is exposed to methods of treatment of such "a nature as to annihilate or destroy the vitality of whatever living "organisms might previously have been present."

Notwithstanding that the terms in which these conclusions are expressed may be open to cavil, any candid person who is fairly acquainted with the discussions which have taken place during the twenty years which have elapsed since they were arrived at, will readily admit that it would have been better for pathological science if they had not been so much overlooked, for the facts on which they are based are quite irreconcilable with the often too carelessly received assumption, that the process of septic infection is dependent on the development of a living contagium.

It was not for the purpose of giving new and additional weight to the testimony of Professor Panum (as to the accuracy of which I could not entertain a moment's doubt) that I undertook the present inquiry, but chiefly in the hope that proceeding from the point to which he had attained, I might be able to advance a step further. I anticipated that whether the poisonous agent was simply a chemical product of this septic process or was endowed with organic form, I could be certain of obtaining it in a condition of great concentration by adopting a method founded on Panum's, and that I should thus be in the most favourable position for investigating its properties and physiological actions.

The question that specially interested me was that of its solubility. In my researches on contagium, published in 1870, I had arrived at the conclusion, which I think I may venture to say has now been very generally accepted, that every contagium consists ultimately of particles not soluble in water. It being admitted that the deleterious agent in septichæmia does not consist of living organisms, it appeared to me possible

No. 1.

On the Properties of the Septic Ferment, by Dr. Burdon Sanderson.

and indeed for several reasons probable, that it would be found to resemble the contagia in being particulate, *i.e.*, that the material, although in the ordinary sense soluble in water, might yet consist of particles so minute as to be incapable of so scattering light as to render the liquid in which they are suspended opalescent, and to be irremovable by any of the ordinary methods of filtration.

In order to determine this important question I filtered liquids prepared in the same way as those of Panum through porous porcelain under pressure, employing a method which will be fully described in the following pages. The result was in so far in accordance with my expectations that I found that changes were produced in the liquid extract which were of such a nature as to deprive it simultaneously of its offensive smell, its poisonous action, and of its remarkable power of generating bacteria. That these three changes stood in anything more than concomitant relation to each other cannot of course be asserted; there is no sufficient ground for regarding them as attributes of one and the same substance.

Before filtration, the extract, notwithstanding that it is perfectly limpid, always exhibits under high powers of the microscope, certain sharply-defined particles. These bodies, which are of such extreme minuteness as to be only just within the limits of microscopical visibility, present no recognisable constant characters either of form or size, so that I am entirely unable to attribute to them any morphological significance. They are entirely absent in liquids which have been passed, even once, through porous porcelain.

The fact has now been proved that virulent septic liquids, even when absolutely free from bacteria or their germs, can be deprived of their virulence by filtration through porous porcelain, but the greatest caution must be used in drawing inferences from it.

The only safe form indeed in which any conclusion can be expressed on the subject is the negative. From the mode of preparation, it can scarcely be supposed that the agent is a living organism. It can further be stated that it is not an albuminous compound, for the absence of bodies of this class is proved by the chemical properties of the liquid before filtration. Its complete removal by filtration renders it probable, but by no means certain, that it is not a crystalline body, soluble in water. The only group of bodies to which its properties suggest comparison is that of the so-called "unformed ferments."

EXPERIMENTAL INVESTIGATIONS.

Preparation.—A quantity of finely-divided fresh muscle was macerated in water for 14 days. The liquid was then strained off and evaporated to dryness on the water bath. The residue, reduced to a fine powder, was digested for an hour or more in seven parts of cold methylated spirit, and afterwards boiled for ten minutes in the spirit. It was then collected on a filter and carefully dried at a temperature of 80° C. until it had entirely lost the alcoholic odour. The insoluble alcoholic residue thus obtained was digested for an hour in from eight to ten parts of cold distilled water, and filtered immediately before use.

Chemical Character.—When prepared in the above manner the liquid is nearly limpid and of a pale straw tint. It has a disagreeable odour and a slightly acid re-action. Its specific gravity is about 1,024,* and it yields on evaporation at 100° C. from two to two and a half per cent. of solid residue.† When heated it becomes slightly turbid or

* The specific gravity varied in different specimens from 1020·9 to 1029·7.

† The mean of five estimations of quantities prepared at different times was 2·1604 °/₀

milky, but on the addition of a few drops of nitric acid again becomes perfectly clear. The addition of acetic acid and potassium ferrocyanide produces no reaction. Heating the extract after adding a few drops of nitric acid slightly deepens the colour, and the addition of a few drops of ammonia, after cooling, causes a deposit which, under the microscope, is seen to consist of feathery crystals, having all the characters of ammonio-magnesic phosphate. None of the other tests for albuminoid substances gave any indication of their presence.

Organic Characters.—The freshly-prepared liquid contains no bacteria, but a greater or less number of very minute shining spheroidal motionless bodies are constantly found in it, to the presence of which its faint opalescence is doubtless due. Exposure to the air, even for a very short time, is sufficient to induce the presence of bacteria. When the extract was kept in sealed tubes, at a temperature of 38° C., bacteria developed in it with extraordinary readiness.

It thus appears that the septic extract is remarkably fertile in relation to bacteria, *i.e.*, that these organisms originate in it with very great facility. In this respect it resembles those artificial cultivating liquids containing peptones which have been lately employed by Huizinga, Gscheidlen, Samuelsohn, myself, and others in experiments relating to the question of spontaneous generation. That, when freshly prepared, it is free from living organisms can scarcely be doubted, for not only does the most careful microscopical examination fail to bring any such organisms into view, but the material from which the extract is prepared has been immediately before thoroughly boiled in alcohol, a process which bacteria can scarcely be supposed capable of surviving.

In order to ascertain whether the extract, although free from living bacteria, owed its fertility to its containing particles of such minuteness as not to impair its transparency, the following experiments were made :—

First Series.—1. Two tubes, about four inches long, were drawn out and heated in the flame of the blow-pipe to a red heat. They were then sealed hermetically in the usual way. On cooling they were partially filled with the extract by breaking off their finely-drawn ends under the surface of the liquid, and were immediately sealed up by the blow-pipe. No. 1 was then placed in the warm chamber, at a temperature of from 35° C. to 38° C. Its contents were perfectly transparent. At the end of twenty days the liquid had become turbid, and on opening the tube the gaseous contents escaped explosively. The liquid was still slightly acid ; it was very fetid and teemed with organisms, namely, short rods, dumb-bells, and spheroids. Tube No. 2 was, previously to being placed in the warm chamber, heated to 110° C. and became slightly milky. On being opened at the same time as No. 1, there was no evolution of gas, and the liquid remained free from organisms.

Second Series.—Four vacuum tubes were prepared in the same manner as those used for the former experiment, and precisely the same method of filling and sealing was adopted. No. 1 was filled with freshly-prepared pyrogenic extract. No. 2 contained the extract filtered once through a porous cell.* No. 3 contained extract which had been

* The porous cells employed for filtration are the cylindrical ones in common use for voltaic elements. The filtration is effected as follows: The liquid to be filtered is introduced into a beaker just large enough to contain the cell. Into the mouth of the cell an india-rubber cork is fitted, perforated by a glass tube. The outer end of the tube is brought into communication with a mercurial air pump by means of a flexible connector of thick-walled vulcanised india rubber. The cell so attached is

filtered twice through a porous cell. In No. 4 was extract which had been passed three times through a porous cell.

These four tubes were placed in the incubator at a temperature of 38° C., and were examined on the tenth day. No. 1 exploded slightly, when its neck was broken off. The liquid was turbid, and filled with actively moving organisms, viz., short rods, dumb-bells, spheroids, and a few short chains. No. 2 exploded but very slightly. To the naked eye its contents did not present any marked turbidity, but when examined microscopally a small number of the same kind of organisms was found as in No. 1. Tubes 3 and 4 contained no organisms.

In order to determine whether the extract, though itself free from living bacteria, possesses, even in the fresh state, the power of determining their development in other liquids, the following experiments were made by the method of impregnation.*

The cultivation liquid used was serum. In order to obtain it under conditions which would, as far as possible, preclude any accidental impregnation of it by means of organic germs, the following plan was adopted :—A glass tube, closed at one end, heated in the flame of the blow pipe, and having its orifice plugged while cooling with cotton wool, was used for the collection of blood from the artery of a rabbit. During coagulation the plug of cotton wool was again inserted. On the following day the serum (about 8 c. c.) was collected and placed in four test tubes, which had previously been heated in the flame of a Bunsen lamp. Three of these tubes were then impregnated with a single drop of the pyrogenic extract, and their orifices were closed with cotton wool. The fourth tube was not impregnated, but the orifice was closed in the same manner as the others. The tubes were then placed vertically in a shallow dish containing a little water, covered by a bell jar, and introduced into the incubator at a temperature of 30° C.

At the end of two days the three impregnated tubes were quite turbid, while the unimpregnated one remained clear. In the former, microscopical examination revealed the presence of a great number of organisms, viz., spheroids, rods, dumb-bells, and chains. In the latter, no organisms could be detected.

Physiological Action.—In the investigation of the physiological or toxical action of the pyrogenic extract dogs were exclusively employed, for the following reasons :—I had ascertained by preliminary experiments that in the dog the symptoms produced are remarkably constant as well as characteristic. In the smaller rodents (the only other animals at my disposal) I had found not only that the effects are inconstant, but that

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plunged into the liquid contained in the beaker, and exhausted by a few strokes of the pump, the process being repeated, if necessary. In a few hours great part of the liquid will have filtered through the wall of the cells into the interior. The most perfect porous cells were selected. At first very thick cells were chosen, and the filtration was conducted through the lower part of the cell only, but it was afterwards found that by using thinner cells and repeating the process, perfect filtration could be obtained in a shorter space of time. After filtration, the specific gravity of the liquid was reduced to 1008·9 or 1009·21. It still retained its slight acid re-action, but was nearly colourless and odourless. Cells once used for filtering could be employed again after calcination. When the liquid was passed through three new porous cells in succession it was always found to be inert.

* This method consists in adding a drop of any liquid or substance to be tested as to its fertility, to some other so-called "cultivation liquid," in respect of which it is known that, although capable of supporting bacterial life, it is not endowed with the property of originating it. My first experiments by this method were made in 1870 with Pasteur's solution. Subsequently I used Cohn's solution, which differs from Pasteur's chiefly in the absence of cane sugar. For the present purpose serum was preferable, as being nearer in its character to the liquid under investigation.

in these creatures the febrile process differs in respect of features more or less essential, from the same process in man; and in particular that, for reasons fully explained in my paper on fever, temperature cannot be used in them as a criterion of the intensity of the febrile disturbance.

The mode of introducing the pyrogenic extract into the circulation was as follows:—A subcutaneous vein having been exposed to the extent of about an inch, the flow of blood was arrested in it temporarily by compression with the finger, the vein wall was pierced by the cannula of a syringe for hypodermic injection, of which the capacity was 5·16 cub. cent., and the requisite quantity was injected.

If more than 5 cub. cent. were required, the syringe was disconnected and refilled without disturbing the cannula. After the injection the cutaneous incision was brought together with sutures, and always healed satisfactorily.

As the purpose of this investigation was to determine to what extent the activity of the septic extract is dependent on constituents which can be removed by mechanical means, it will be convenient first to give an account of the symptoms produced by the clear extract when prepared as above described, and repeatedly filtered in the usual way through paper, and the same liquid after it has passed through porous porcelain under pressure.

Section I.

Action of the filtered Extract.

The symptoms produced in dogs by the injection of pyrogenic extract were as follows:—The first symptom was shivering, more or less marked, continued for several hours, and accompanied by a rise of temperature amounting to 2° C., or even 3° C., the maximum being usually reached at the end of the third hour after the injection. Bilious vomiting and mucous diarrhœa were always observed about the time at which the temperature was highest, and continued for some time after it began to fall. In addition to the mucous diarrhœa there was frequently a considerable amount of intestinal hæmorrhage, and it was characteristic that the introduction of the thermometer into the rectum produced on each occasion tenesmus. In most cases thirst constituted a marked symptom, but if the animals were allowed to drink much water the retching and vomiting were greatly increased, and the water was brought up again almost as soon as swallowed. Usually after the end of the third hour, but never later than the end of the fourth hour after the injection, the symptoms began to subside, the temperature fell almost to the normal, and the vomiting and diarrhœa ceased. In the course of five or six hours with the exception of an occasional slight shiver and some languor, the animal appeared to have recovered. In less than twelve hours after the injection the animals had become quite lively and were anxious for food.

By way of example, the following case, in which a full grown and healthy animal was employed, may be given as very fairly representing the other experiments.

A healthy full-grown dog, weighing 8,264 grammes was infected by injecting 10·32 cub. cent. of pyrogenic extract into the saphena vein in the manner already described. His temperature, previously to the injection, was 38°·7 C. The injection was completed at 4 o'clock p.m., and immediately after the animal became very restless, was salivated, and appeared to suffer from nausea. One hour after the injection the temperature had risen to 40°·1 C., and on withdrawing the thermometer

from the rectum a small quantity of mucus was passed. The animal appeared very ill, was shivering, and at each inspiration uttered a peculiar whining moan. At 6 p.m. the temperature had increased to 40°·4 C., and now there was well marked mucous diarrhœa with tenesmus. The highest temperature, viz., 41° C. was observed at 7 p.m., all the other symptoms, but especially the shivering, being well marked. Four hours after the injection the temperature had fallen to 40°·4 C., but the other symptoms continued, and vomiting had also occurred. During the fifth hour the temperature further declined to 39°·9 C., the shivering was subsiding, the respiration had assumed a normal character, but the animal still appeared suffering. He was very dull, and refused food, stood with his back arched and tail depressed, his nose was hot and dry. On the following morning his temperature was normal, and except that he was somewhat dull, he appeared quite recovered.

In the preceding experiment about one cubic centim. and a quarter of extract per kilo. of body weight of the animal, was injected. As the symptoms were characteristic but not excessive, and the recovery was complete and prompt, this proportion was adopted in all future cases. When, however, it was necessary to employ ill-grown or ill-nourished animals, a diminution of the dose was made in consideration of these circumstances, the object being to produce the required result without exceeding it. In a long series of experiments these results were observed without fail, no case presenting itself in which there appeared to be insusceptibility to the action of the poison, and few only in which the symptoms produced were excessive.

The results of similar observations on other animals are shown in the following table in which the date of each experiment, the weight of the animal used, the quantity injected into the circulation, the temperature of the animal before injection, and finally its temperature at successive periods of observation, one, two, three, and four hours after injection are shown.

Table I.

—	Date.	Weight of Dog.	Dose.	Normal.	1st hour.	2nd hour.	3rd hour.	4th hour.
No. 1	Sept. 1st 1874	8,264 grms.	10·32 c.c.	38·6	39·1	40·6	40·2	39·4
„ 2	„ 5th „	4,837 „	5·16 „	38·6	40·0	41·0	41·0	40·8
„ 3	„ 28th „	8,100 „	10·32 „	38·8	40·2	40·6	41·2	—
„ 4	Dec. 23rd „	4,082 „	5·16 „	39·0	39·8	41·2	40·8	—
„ 5	„ 28th „	7,937 „	10·32 „	39·0	40·8	41·9	42·2	42·3
„ 6	Jan. 5th 1875	6,191 „	7·56 „	38·8	39·3	40·0	40·5	40·4
„ 7	March 19th „	6,803 „	8·7 „	38·6	39·8	40·2	40·6	40·4
„ 8	April 16th „	3,061 „	4·0 „	39·0	40·6	40·8	41·3	39·6
„ 9	„ 21st „	6,100 „	5·16 „	39·0	41·3	41·2	40·6	40·4
„ 10	May 4th „	3,130 „	5·0 „	38·8	39·2	39·8	40·0	40·8
„ 11	June 1st „	7,257 „	9·5 „	38·6	39·4	40·7	41·4	40·6
„ 12	Jan. 21st 1876	7,937 „	10·32 „	38·8	39·6	—	40·8	40·6
„ 13	Feb. 10th „	6,350 „	8·0 „	39·0	40·0	40·5	40·6	40·4
„ 14	March 20th „	5,556 „	5·16 „	38·8	40·2	41·0	—	—

In all the tabulated cases the symptoms were in strict correspondence with those already described in case No. 1. But in one or two instances, not included in the table, the symptoms which presented themselves were different. The animal passed rapidly into a state of collapse, indicated by the fact that the bodily temperature fell. The fall of temperature was accompanied by bilious vomiting, mucous diarrhœa, and

intestinal hæmorrhage, and death followed in a few hours. The following case may be given in illustration :—

A healthy dog, weighing about 6,350 grammes, was injected in the tibial vein with 9 cub. cent. of the extract. Before injection the temperature of the animal was 38°·8 C., while an hour after, it had risen to 39°·6 C. and vomiting had occurred. At the end of the second hour the temperature had fallen to 38°·2 C. and the animal was in a state of collapse. There was mucous diarrhœa and the sphincter ani was quite relaxed. The temperature gradually sank to 32°·6 C., when, at the end of the fifth hour the animal died. During the whole period quantities of ropy saliva flowed from the mouth, and masses of mucus passed from the intestine, the breathing being laboured and very irregular. After death the mucous membrane of the intestines was found to be intensely hyperæmic, studded with hæmorrhagic patches, and covered by a layer of blood-stained mucus, which could be easily detached.

The particulars of the above and other similar instances are given in the following table :

Table II.

No. of Animal.	Date.	Weight of Dog.	Dose.	Normal Temp.	Temperature after Injection.						Result.	Symptoms.
					1 hour.	2 hours.	3 hours.	4 hours.	5 hours.	6 hours.		
	1875	grms.	c.c.									
1	April 12th	6,350	9	38·8	39·6	38·2	37·2	35·6	32·6	—	Death in 5 hours.	Vomiting, diarrhœa, collapse.
2	June 4th	4,762	6	38·8	37·6	36·8	34·8	34·6	34·8	—	Do.	Mucous diarrhœa.
3	„ 21st	4,989	5·16	38·8	39·1	37·2	39·6	39·4	39·0	—	Recovery	Salivation, shivering, and bilious vomiting.
4	„ 22nd	4,780	5·16	38·8	38·4	37·2	35·8	—	34·5	32·0	Death in 6 hours.	Collapse.

Among these cases the third is specially worthy of notice as intermediate in its character between the ordinary case in which the bodily temperature rises to that of pyrexia, and the more severe ones. The general symptoms were exceptionally severe, but the temperature was throughout normal. If the action of the poison had been milder, it would have risen; had it been more severe than it actually was, it would have fallen.* The following instance differs from the others only in the prolongation of the symptoms. The injection was effected in the afternoon; late in the evening recovery seemed probable, but it did not continue.

A dog, weighing about 3,175 grammes, had 5·16 cub. centims. of the extract injected into the tibial vein. At 3.30 p.m., before the inoculation, which was then effected, the temperature was 38°·8 C. At 4.30, it was 37°·8 C., and vomiting and mucous diarrhœa had occurred. An hour later there was marked tenesmus, and the temperature was 35°·9 C. At 6.30, the temperature was 35°·8 C., but after this a slight re-action

* This illustrates a statement made in my paper on the Process of Fever, viz. : that in a certain sense it is possible to have fever without pyrexia. In the animal No. 3., which received the same dose of the same pyrogenic agent as the others, in which the temperature rose to febrile (104° or 106° Fahr.), the physiological process was, notwithstanding that there was no pyrexia, as truly febrile as in the others.

took place, and the temperature rose a little, being 36°·2 C. at 8.30 p.m. The animal however was in a prostrate condition, and was unable to stand. The introduction of the thermometer into the rectum caused excessive straining, and protrusion of the intestine. On removing the thermometer it was seen to be covered with blood-stained mucus. The animal was found dead on the following morning. The only striking post-mortem appearance was the intense hyperæmia of the mucous membrane of the intestine, the contents of which were coloured with blood.

The two sets of cases referred to above as severe and mild respectively, differed so much in their heat phenomena that the question might arise whether the severity of the symptoms observed in certain cases was not attributable either to peculiarities in the animals used, to the mere bulk of liquid injected, or to some other cause. That the differences of effect were mainly, if not entirely dependent on the quantity of virulent matter introduced, may be learnt by comparing the symptoms observed when the same dose of the same liquid was administered to the same animal at one time in a concentrated, at another in a diluted state. This comparison gave the following results :—

1. A strong healthy dog, weighing 6,803 grammes, was injected with 8 cub. cent. of the ordinary extract on March 19. The normal temperature was 38°·6 C. At 5.15 p.m., one hour from the injection, it had risen to 39°·8 C., and an hour later to 40°·2 C., the rise being accompanied with shivering, vomiting, and diarrhœa. These symptoms were still present at 7.15, when the temperature had reached 40°·6 C. After another hour the shivering was subsiding, and the temperature had fallen to 40°·4 C. On the following day the temperature was normal, and the animal seemed quite well.

2. On April 28th, the same animal was injected at 3.30 p.m. with the same quantity of liquid, the temperature being just previously 39° C. During the following three hours the temperature was successively 39°·7 C., 40°·6 C., and 40°·6 C. At 7.40 p.m., it had fallen to 40°·2 C. During the whole of this time the animal was very ill, and the usual symptoms, diarrhœa, vomiting, and shivering were present. On the following morning the animal had recovered.

3. On May 5th the same animal was again employed for experiment, and at 5.45 p.m. eight cub. cent. of a stronger extract were injected into the jugular vein. This liquid had been prepared in the same way as that used for the former experiments, but had been evaporated on the water bath at a temperature of from 80° to 85° C. to half its original volume. The normal temperature of the animal was 39° C. After injection the temperature in successive hours was as follows :—At 6.45 p.m. 37°·7 C., at 7.45, 37°·6, at 8.45, 37°·8, and at 9·30, 37°·6 C. During the whole period the animal was shivering, had diarrhœa, and passed blood-stained mucus. At the end of the time there was marked tenesmus and extreme prostration. On the day following the injection the temperature was normal, but the animal was evidently still ill, refused food, and passed a quantity of blood, showing that the intestinal hyperæmia which is so marked a feature, had existed in its fullest intensity. On the third day there was no hœmorrhage from the bowel, but the animal was emaciating rapidly. On May 8th, at 4 p.m. it was dying, and the temperature was as low as 28° C. The specific gravity of some blood withdrawn from the carotid artery did not exceed that of serum, being only 1033·4.

The only noteworthy post-mortem appearance was the extremely pale and ex-sanguine condition of the tissues. No exudation was found in the pleura or peritoneum. The mucous membrane of the intestines was not ulcerated, but it was of a pale colour and easily detached.

Section II.

Action of the Extract after Percolation through Porous Porcelain.

In the first experiment the Dog No. I. was employed, in which, as before stated, the character of the symptoms produced by an ordinary dose (10 centims.) of the fresh extract had been precisely ascertained. This animal received in all four doses of the extract, of which the first, second, and fourth were filtered in the ordinary way, the third through porous porcelain. The results were as follows:—

Table III.

No. of Animal.	Date.	Weight of Animal.	Quantity Injected.	Extract.	Normal temp.	Temperature after Injection.				Symptoms.
						1 hour.	2 hours.	3 hours.	4 hours.	
I.	Aug. 28th, 1874	8,264 grm.	10·32 c.c.	Unfiltered	38·7	40·1	40·4	41·0	40·4	Shivering and vomiting. Temp. at 5th hour, 39·9.
	Sept. 1st, 1874	—	„	„	38·6	39·1	40·6	40·2	39·4	Shivering very much.
	„ 9th „	—		Filtered	38·4	39·2	38·5	38·3	38·4	No symptoms produced.
	„ 14th „	—	„	Unfiltered	38·8	39·9	41·4	41·5	40·8	Shivering and tenesmus. Temp. at 5th hour, 40·2.
II.	Dec. 30th, 1874	5,329 grm.	8·7 c.c.	Unfiltered	38·8	39·4	40·5	41·6	41·2	Vomiting and shivering.
	Jan. 7th, 1875	—	„	„	38·8	40·0	40·6	41·4	41·6	Shivering and mucous diarrhœa.
	„ 14th „	—	„	„	38·5	40·2	41·0	41·4	41·0	Do. do.
	„ 2nd „	—	8·7 c.c.	Filtered	39·1	39·3	39·0	38·8	—	No symptoms observed.
	„ 11th „	—	„	„	38·4	39·0	39·3	38·8	38·8	Do. do.
III.	„ 2nd „	4,876 grm.	8·7 c.c.	Unfiltered	39·6	40·7	41·2	40·7	40·4	Vomiting and shivering.
	„ 11th „	—	„	„	38·6	39·6	40·4	40·8	40·6	Salivation, vomiting, and dysenteric evacuations.
	Dec. 31st, 1874	—	8·7 cc.	Filtered	38·7	39·0	39·2	39·3	39·0	No symptoms produced.
	Jan. 7th, 1875	—	„	„	38·8	39·6	39·8	39·6	39·2	Do. do.
	„ 14th „	—	„	„	39·0	39·4	39·8	40·0	—	Do. do.
IV.	Feb. 19th, 1876	7,030 grm.	9 c.c.	Unfiltered	39·0	39·4	40·7	41·2	40·4	Shivering.
	April 1st „	—	10·32 c.c.	„	39·0	39·4	40·6	40·3	—	Diarrhœa and vomiting.
	„ 8th „	—	15·48 c.c.	„	39·1	40·1	40·6	41·0	—	Do. do.
	Sept. 16th, 1876	—	9 c.c.	Filtered.	39·2	38·6	38·8	39·0	—	No symptoms produced.
	April 4th „	—	15·38 cc.	„	39·2	39·3	39·2	39·2	—	Do. do.

The transitory and very inconsiderable rise of temperature which followed the third injection in Dog I. is of no significance, for it is known by observation that it is not possible to inject 10 centims. of even the most indifferent liquid without producing this slight disturbance. It is to be noticed that by the end of the second hour the temperature had returned to the standard of health, and throughout the whole period of

observation the animal was in an absolutely normal condition. *It was lively, answered readily when called, and showed no indication of being in the slightest degree affected by the injection.*

The result of three similar series of experiments are exhibited in the same Table. They prove in the plainest way that whatever may be the nature of the poisonous agent, it admits of complete removal by mechanical filtration. By way of supplement to this observation, two series of experiments have been recently made in which an ordinary infusion of putrid muscle was substituted for the aqueous extract of the alcoholic precipitate. I subjoin the tabular summary of these experiments in the same form as the others. They have no bearing on one of the questions discussed in the introduction to this paper, viz., that of the participation of living bacteria in the production of the toxical action; for in this case the liquid swarmed with these organisms. But they exhibit quite as clearly as the other experiments, that if the body to which a putrid infusion owes its poisonous action, is soluble in water at all, it is so in such a sense that it is unable to pass through porcelain.

Table IV.

No. of Animal.	Date.	Weight of Dog.	Quantity injected.	Extract.	Temperature.					Symptoms produced.
					Normal.	1 hour.	2 hours.	3 hours.	4 hours.	
No. 1.	March 1, 1876 -	7,030 grm.	8 c. c.	Unfiltered	39·0	40·6	40·9	41·4	41·6	Vomiting and tenesmus.
	„ 17 „	—	15·48 c. c.	„	39·2	40·2	41·1	41·2	41·4	Vomiting, diarrhœa, and dysenteric evacuations.
	„ 16 „	—	„	Filtered.	39·0	39·6	39·2	39·2	—	No symptoms.
No. 2.	March 7, 1876 -	7,937 grm.	10·32 c. c.	Unfiltered	39·0	39·8	41·0	41·4	40·8	Bilious vomiting and diarrhœa.
	„ 10 „	—	10·32 c. c.	Filtered.	38·6	39·6	39·2	39·2	39·0	No symptoms.
No. 3.	March 7, 1876 -	6,350 grm.	8 c. c.	Unfiltered	39·2	40·2	39·8	40·2	—	Vomiting and tenesmus.
	„ 10 „	—	8 c. c.	Filtered.	39·1	39·8	39·4	39·2	39·2	No symptoms.

No. 2.

Dr. Klein in correction of former Paper on Sheep-pox.

Note by Dr. E. Klein, F.R.S., on the Mycelium described in his Paper on Smallpox of Sheep.

In my paper published in 1874 in No. III. of this series of reports, I described and figured on pages 55, 56, 58, and 59, the presence, in the lymphatics of the skin of the pock, of what I regarded to be the mycelium of a fungus which I termed *Oidium variolæ*. Similar features were described and figured in the cavities of the primary and secondary pustules.

My attention has been drawn by Dr. Charles Creighton to appearances, in many respects similar to those described by myself, which he found in preparations of tissues altogether removed from the suspicion of containing fungoid growths of that or any other character; namely, in sections through hardened mammary glands.

A comparison of the two kinds of specimens convinced me that the appearances represented in my figure XI. are not due, as I supposed, to a mycelium in the cavities of the primary pustules, but are products of coagulation of some albuminous or kindred material by the reagent (dilute chromic acid and spirit) that had been employed for hardening the object in question.

The vegetable nature of the other structures—viz. those represented in figs. V., VI., VII., and VIII. (*i.e.* the supposed mycelium in the lymphatics of the skin of the pock), as well as those in fig. X. (*i.e.* the mycelium in the cavities of the secondary pustules)—becomes therefore very doubtful. My doubt as to these being also produced by coagulation is based partly on the similarity between the last-named features and those undoubtedly non-vegetable objects in Dr. Creighton's specimens and also in my fig. XI., and partly on the following circumstances: –(1.)I have lately ascertained that blood, especially in febrile conditions, which is contained in blood-vessels of tissues that had been subjected, in a fresh condition, to the hardening fluid (*e.g.*, chromic acid) presents appearances very similar to branched mycelium-threads to which are attached numerous conidia; the presence of more or less unaltered blood-corpuscles proves their true character. (2.) I have likewise seen that blood-plasma containing globulin or parts of blood-corpuscles, when in lymphatic vessels or kindred spaces, show sometimes in the course of coagulation similar appearances. Whether the greater number of the thread-like structures is due to fibrin or to blood-corpuscles I cannot determine as yet; but it seems to me that both is the case.

In the case of *Variola ovina* it is therefore probable that the supposed mycelium in the lymphatics is due to coagulation of some substance directly connected with blood. My statement, however, remains that in the early stages the lymphatics of the affected skin are filled with micrococci. Of the reality of these organisms (described also by Weizert in the lymphatics of the skin in human variola) there cannot be any kind of question.

No. 3.

Report on the Minute Anatomy of Scarlatina, by Dr. Klein.

This paper contains the results of the microscopic examination of the following organs in Scarlatina: skin, kidney, the tongue, palate, tonsils and pharynx, the œsophagus, stomach, small and large intestine, the larynx and trachea, the salivary and pancreas gland, the liver, the lymphatic glands, and lastly, the spleen. Of these, the skin has been examined in 20, the kidney in 23, the organs of the throat, the liver, spleen, and lymphatic glands have been examined in 8, and the alimentary canal in 3 cases.

Before proceeding to state the results of previous observations as well as my own, it is advisable to give a short account of the cases that have been the source of the above material.

I.—Material for Anatomical Examination.

The following cases have all been under the care of my friend Mr. Shirley F. Murphy, resident medical officer to the London Fever Hospital, to whose great kindness I owe all the material for the present research.

Case 1.—A. B., ætatis 6, was admitted into the London Fever Hospital on January 16th, 1876, after having been ill one day. On admission, evening temperature (E. T.) 104°, morning temperature (M. T.) 106°. Had two convulsive fits in the morning of 17th at 3 and at 8 a.m.; died in the evening of 17th, *i.e.*, after two days' illness. No albumen in urine after death.

Case 2.—J. W., æt. 8, died on April 8th, 1875, some hours after admission into the L. F. H., after three days' illness.

Case 3.—F. C. S., æt. 8, was admitted into the L. F. H. on July 10th, 1875, having been ill two days. On day of admission, M. T. 102°·2, E. T. 104°·6. The whole of body covered with dark s arlet rash. On 11th, M. T. 105°·2, E. T. 104°. On 12th, M. T. 104°·8 ; died during the day, *i.e.*, after four days' illness.

Case 4.—C. S., æt. $4\frac{3}{4}$, died on January 24th, 1876, within four hours of admission into the L. F. H., after four days' illness.

Case 5.—A. P., æt. 8, died after four days' illness.

Case 6.—F. T., æt. 11, was admitted into the L. F. H. on January 16th, 1876, having been ill two days. T. 104°·2 ; on January 17th, M. T. 104°·3. Delirious ; dusky rash over body ; E. T. 104°. On the 18th, T. 104°·4 ; very delirious and prostrate ; dusky rash ; albumen in urine ; died in the afternoon, *i.e.*, after four days' illness.

Case 7.—T. H., æt. 28, was admitted into the L. F. H. on April 12th, 1875, after having been ill three days. Faint scarlet rash ; E. T. 102°·4. On 13th, M. T. 102°, E. T. 101°·8. On 14th, M. T. 100°·8, was dead early in the morning of 15th, *i.e.*, died after five days' illness. No albumen in urine.

Case 8.—F. T., æt. 4, was admitted into the L. F. H. on November 29th, 1875, having been ill two days. On admission had a dark rash over whole of body. On 30th, E. T. 103°·4. On December 1st, M. T. 103°·2, E. T. 103°·8, no albumen in urine. On 2nd December, M. T. 103°. Rash very dark ; died on the 3rd, *i.e.*, after five days' illness.

Case 9.—M. B., æt. 12, was admitted into the L. F. H. on June 28th, 1876, having been ill three days ; dark motley rash ; throat much inflamed ; tonsils sloughing ; glands of both sides of neck enlarged ; delirious ; no albumen in urine. On 29th, M. T. 104°·6, E. T. 104°·8 (after a cold

bath). On 30th, M. T. 105°; died quite suddenly at 3·55 p.m., after five days' illness; no albumen in urine. (For the post-mortem appearances of alimentary canal and mesenteric glands, *see hereafter*.)

Case 10.—M. A. J., æt. 36, was admitted into the L. F. H. on July 10th, 1875, having been ill two days. Has for some time been nursing her child, who was suffering from scarlatina. Slight rash on second day of illness. No rash visible on day of admission; E. T. on July 11th, 105°. On July 12th, M. T. 103°·6, E. T. 103°; no albumen in urine. On 13th, constantly delirious; M. T. 102°·9, E. T. 102°·8. On 14th, M. T. 104°·8, constantly delirious. At noon, T. 106°·2. Died at 3.15 p.m., *i.e.*, after six days' illness. No albumen in urine.

Case 11.—J. B., æt. $1\frac{3}{4}$, was admitted into the L. F. H. on June 1st, 1876, having been ill one day. Died on the 6th of June, *i.e.*, after about six days' illness; albumen in urine.

Case 12.—H. A., æt. 5, was admitted into the L. F. H. on October 9th, 1875; fading scarlatina rash; no history; T. 103°·6. On 10th, M. T. 102°·4; has a raised rash over legs and thighs. On 12th, M. T. 104°, rash fading, injection of skin uniform, E. T. 102°. On 16th, M. T. 104°; much prostrate; died in the morning, *i.e.*, after about seven days; no albumen throughout illness.

Case 13.—J. H. R., æt. 4, was admitted into the L. F. H. on October 26th, 1875, having been ill four days. On admission has no rash, E. T. 102°·4. On 27th, M. T. 103°·8. Constantly delirious. On 28th, very prostrate; died at 11 p.m., *i.e.*, after six days' illness.

Case 14.—T. L., æt. 7, was admitted into the L. F. H. on October 31st, 1875. No history. On admission has scarlatina rash over whole body. T. 101°; on November 2nd, rash still present; M. T. 102°·1, E. T. 103°. On 3rd, rash less. On 4th, rash nearly gone; albumen in urine; M. T. 101°·8, E. T. 103°·6. On 5th, constantly delirious; much prostrate; M. T. 101°·4, E. T. 103°. On 7th, urine still albuminous; M. T. 101°, E. T. 103°·8. On 8th, no albumen in urine; M. T. 102°, E. T. 102°. Died on 9th, *i.e.*, after about ten days.

Case 15.—D. F. S., æt. 2, girl, was admitted into the L. F. H. on November 19th, 1875, having been ill one day. Scarlatina rash on whole of body. On November 21st, no albumen in urine, M. T. 101°·2, E. T. 102°; glands of neck much swollen. Died on 28th, *i.e.*, after ten days' illness.

Case 16.—J. D. S., æt. $3\frac{1}{2}$ (brother of the preceding patient), was admitted into the L. F. H. on November 21st, 1875, having been taken ill the day before admission. Has a bright scarlet rash over whole of body. On 24th, rash fading, M. T. 104°, E. T. 104°. Glands of neck much swollen. On 29th, urine albuminous, M. T. 102°, E. T. 104°·2. Died much exhausted on December the 2nd, *i.e.*, after about 11 days illness.

Case 17.—T. D., æt. 14, was admitted into the L. F. H. on October 6th, 1875, having been ill five days. Has a dark patchy rash and appears much prostrate. E. T. 101°. Died much exhausted on 12th, *i.e.*, after 11 days' illness. No albumen throughout illness.

Case 18.—G. C., æt. 5, was admitted into the L. F. H. on October 15th, 1875. Died in the morning of the 16th, after 13 days' illness.

Case 19.—E. W., æt. 8, was admitted into the L. F. H. on September 28th, 1875, having been ill three days. Died on October 12th, *i.e.*, after 17 days' illness. Urine examined after death contained albumen.

Case 20.—G. W., æt. 10, was admitted into the L. F. H. on December 11th, 1875. No history. On admission has patchy scarlatina rash. Died on 27th, *i.e.*, about the end of third week.

Case 21.—H. G. A., æt. 4, was admitted into the L. F. H. on October 24th, 1875, having been taken ill six days ago. On admission has dusky uniform rash all over body. On 27th, glands of neck much swollen, rash no more to be seen; E. T. 102°. From November 1st until November 6th very restless; on the 7th of November suppuration on left side of neck. Died on the 8th, *i.e.*, after 21 days' illness.

Case 22.—A. W., æt. 6, was admitted into the L. F. H. on November 17th, 1875; was taken ill two days previously. On admission has a bright scarlatina rash over whole body. On 20th, rash still present, much inflammation of fauces; much prostrate; delirious. M. T. 101°, E. T. 102°. On December 9th, glands of left side of neck much enlarged. No albumen in urine. Died on 11th, *i.e.*, after 26 days' illness.

Case 23.—E. F., æt. 9, was admitted into the L. F. H. on September 28th, 1875, having been ill since the previous day. On admission has a bright scarlatina rash over the whole body. On 26th of October urine contained albumen and remained so until the 30th; glands of neck much enlarged. From 31st until 2nd November no albumen in urine. Since the 3rd of November suffered from pneumonia, and died on November 10th, *i.e.*, 44 days since first taken ill from scarlatina.

The material used for microscopic sections was removed from the dead body as soon as possible after death, and hardened in a mixture of two parts of one sixth per cent. chromic acid and one part of methylated alcohol. The hardening process was completed (after about a week) in pure methylated alcohol.

II.—Microscopic Examination of the affected Skin.

A. *With special reference to the above cases.*

I propose to take the different cases in the order of their duration of illness, *i.e.*, in the same order in which they have been enumerated above, commencing with case 1, of two days' duration, and passing on to cases of three, four, five, &c. days' duration; and I propose to describe, in regard of each case, the microscopical appearances of the skin in parts which had been affected with eruption. After the description of the individual cases, a general summary will be given of the changes of the skin in the different periods of the disease.

Case 1.—The epidermis slightly thickened, the layers of the stratum corneum somewhat loosely attached to each other. Many cells of the superficial as well as of the deeper layers of the Rete Malpighii contain double nuclei or nuclei in the act of division, thus indicating that there is probably also a multiplication of the epithelial cells themselves. The chief feature of interest in the epidermis is the presence of cavities of different sizes at the boundary between Rete Malpighii and stratum corneum; they project with a convex surface towards the latter. The larger of them contain a more or less uniformly granular matter, and a few larger droplet-like structures among them. The contents appear in hæmatoxylin preparations of a slight yellowish tint. The granules of the former are of very uniform size, and certainly give one the impression of a collection of micrococci, *i.e.*, zoogloœa. The appearances have been represented very accurately in Fig. II. The question of great importance is, of what nature is the material contained in these cavities? In the first place, it may be merely exuded plasma that has accumulated in cavities in the epidermis, there being, as will be mentioned below, much hyperæmia in the skin; that is to say, it may be that we have before us on a microscopical scale, the vesicles of a

miliary eruption, with their contained exudation coagulated by the hardening agent. I cannot disprove that it is so; I can only say that with the naked eye there was nothing to be observed of a miliary eruption.

Professor Thomas, in his article on Scarlatina (Ziemssen's Cyclopædia of the Practice of Medicine, vol ii., English translation, p. 149 and following), says on page 162, "Miquel reported to the "French Academy that he had inoculated a number of children, who "had never had the disease, with the contents of vesicles from scarla- "tinous patients; thirty hours after, there appeared at the place of "inoculation a red areola, which corresponded in every respect to the "scarlatinous eruption; this redness increased for three days, and "disappeared on the fifth day. The inflammation was not traumatic, "for a second inoculation in the same individual had no effect.' Taking into consideration the present state of the doctrine of contagion, it is interesting to inquire, with regard to the granules present in the epidermis of scarlatinous eruption, whether they possess any definite characters which would permit of their being regarded as micrococci and not merely as coagulated plasma. As has been already stated, the material does not stain blue with hæmatoxylin like many micrococci situated on or near a free surface, but appears, probably by contrast with the violet-blue colouration of the specimen with hæmatoxylin of a slightly yellowish tint. But the fact of its not staining with hæmatoxylin cannot be decisive, as I have not unfrequently seen undoubted masses of micrococci which did not become tinted blue by logwood. It appears to me that this depends on a variety of causes, one of which is the nature of the tissue, another the process to which the preparation had been subjected before it was placed into the staining fluid; thus the masses of undoubted micrococci situated on the surface of the mucosa and in Lieberkühn's crypts of the typhoid intestine, hardened in chromic acid, did not stain at all with hæmatoxylin.

If the granular material in question had stained blue I would not hesitate for a moment to pronounce it to be composed of micrococci; as it has, however, remained unstained it is necessary to see whether there exist other reasons for saying so. The chemical reaction did not yield any positive results, for after subjecting the preparation (section of hardened tissue) to the action of caustic potash (35 per cent.), or dilute acetic acid, the granular matter remained unchanged, but then there appeared in the preparation so much additional granular matter—occasionally quite as uniformly and regularly granular as the former—that it is quite impossible to arrive at a definite conclusion.

Thus it is impossible to say anything else but that the nature of the material in question cannot at present be established with certainty.

Besides these cavities containing the granular material there are other smaller cavities, not larger than one or two epidermis-cells, which do not contain any formed matter, being merely spaces between the most superficial cells of the Rete Malpighii which are being converted into horny scales; by the confluence of these spaces in a horizontal direction the stratification is effected of the superficial layers.

In the Rete Malpighii are found lymphoid corpuscles, possessing one or two small nuclei deeply stained by hæmatoxylin, and thus easily distinguishable from the nuclei of the epithelial cells. These lymph-corpuscles may be traced from the papillary layer of the corium, and it must be assumed therefore that they migrate into the epidermis.

We shall return to this question of the infiltration of the epidermis or epithelium with wandering cells from the sub-epithelial membrane more fully

hereafter when dealing with the changes of the mucous membrane of the throat.

At some places these wandering or lymph-corpuscles are only to be met with singly, at others they form small collections.

The chief sign by which the increased thickness of the Rete Malpighii may be recognised at once is the dimensions of the interpapillary processes, these being somewhat longer and more prominent than in the normal skin. Hence also the papillæ of the corium are more marked than in the normal condition.

In connexion with the thickening of the Rete Malpighii may be mentioned the increase of the nuclei of the epithelial cells lining the neck and mouth of the hair follicles; in many instances the nuclei are seen in couples or triplets.

The superficial part of the corium, *i.e.*, the papillary body, contains a greater number of nuclei than normally. They are generally arranged along the venous and capillary vessels, and may be divided into two kinds: (*a*) ovoid transparent finely granular nuclei belonging to the endothelial wall of blood vessels or lymphatics, and (*b*) rounded nuclei, either single or double, staining much deeper in hæmatoxylin than the former, and being surrounded in many instances by a zone of granular protoplasm. The former, viz., the nuclei of endothelial structures, appear more numerous than in the normal parts of the skin; the latter are more abundant in the most superficial parts of the papillæ, whence they find their way into the Rete Malpighii.

In connexion with this last-named fact I wish to mention an appearance which is commonly met with in the Rete Malpighii of the scarlatinous skin as well as in the epithelium of the mucous membrane of the throat in scarlatina, in some parts more distinct than in others. It is this: the individual cells of the Rete Malpighii, chiefly in the deepest and middle strata, appear in our sections distinctly separated by clear transparent canals, intercellular canals, which at some places expand into small lacunæ. Into the intercellular canals the ridges of the ridge-and-furrow cells may be seen to project, without, however, passing right across the canals as represented by Bizzozero, who first described this appearance in the epithelium, and regarded it as a normal feature. From what I stated just now I do not of course with Lott go so far as to say that these intercellular canals do not exist, but on the other hand I do not go the whole length with Bizzozero either, who maintains that those canals in their great distinctness are normal structures. It is beyond doubt that they are very distinct if the sub-epithelial membrane, corium or mucosa, is in a slight inflammatory condition, *i.e.*, if the latter as well as the epithelium are irrigated by abnormal quantities of plasma. Owing to this circumstance the lymph-canal system of the papillary body is very distinct. From these facts it seems to me probable that the intercellular substance (cement-substance) of the epithelium, which according to the recent observations of Thoma, Arnold, and Küttner represents the passages through which fluid and formed matter is carried from the sub-epithelial membrane into the epithelium, becomes more fluid and more copious, as far as space is concerned, during this abnormal irrigation; so that the intercellular canals, which contain an abnormal quantity of intercellular substance, appear in hardened specimens much distended and more distinct than in the healthy state. As we shall see very distinctly in connexion with the mucous membrane of the throat, the wandering lymph-cells of the mucosa pass from this latter into the epithelium through the intercellular canals, and accumulating in them cause the appearance of smaller or larger cavities or vesicles in the

epithelium. Fig. XIX., which is taken from a section through a papilla of the tongue of a scarlatina case (*see* explanation of figure), shows the intercellular canals distended at some places to smaller or larger cavities containing wandering cells.

As I mentioned before, we shall meet with these appearances, viz., great distinctness of intercellular canals, and in them migrants which have travelled thither from the subepithelial membrane, very often hereafter in the skin, and especially in the throat, and I wish to repeat that I regard these facts as a consequence and a symptom of the general inflammatory condition of the corresponding membranes.

Among the migratory cells found in the superficial layers of the corium are some that are filled with yellowish brown pigment-granules. From the corium the pigment-granules may be traced into the deepest stratum of the Rete Malpighii, where they form lumps situated in the upper part of the deepest cells, *i.e.*, externally to the nucleus.

The bulb of some large hair-follicles is possessed of several digitate processes composed of small nuclear cells, which form a continuity with, and are therefore outgrowths of, the epithelium of the external root-sheath. The sweat glands show the following changes: the nuclei of the epithelium lining the first part of the duct, *i.e.*, that part which comes off from the coiled tube, are very much increased in number, but also the nuclei of the epithelial cells lining this latter are at some places more numerous than at others. The lumen of the coiled tube is distinct. A few lymph-corpuscles may be seen around the sweat glands; they are, however, much more abundant around the hair-follicles.

The blood vessels appear distended and filled with blood corpuscles, amongst which may be found masses of fibrin.

There is an important point to be mentioned as regards the arteries; it is namely this: in some parts of the muscular coat the nuclei are more abundant than in others, owing to the transverse division of the ordinary staff-shaped nuclei of the circular muscle-fibres into two or three smaller oblong nuclei placed end to end with their long axis. This fact, viz., the division and multiplication of the nucleus of the unstriped muscle fibres of the arterial wall will be mentioned hereafter repeatedly in connexion with the kidney and throat.

Having dwelt at some length on the changes of the epidermis and corium in this case, it will be possible for me to be brief in the description of the other cases. Thus by saying that the epidermis is increased in thickness, the concomitant symptoms are understood at the same time, *e.g.*, nuclei in the act of division or already divided, interpapillary process lengthened, &c., &c.

Case 2.—Epidermis increased in thickness, especially the Rete Malpighii. Intercellular canals discernible; not only the deepest stratum of the Rete Malpighii but also the strata next to it are composed of cells elongated in a direction vertical to the surface. The chief point of interest in the epidermis is represented by the local thickening of the stratum lucidum of Philippi and Schrön, *i.e.*, the horny homogeneous layer between the proper stratified stratum corneum and Rete Malpighii, which is present generally only in some parts of the epidermis, and then only as an exceedingly thin transparent stratum; it contains occasionally the last rudiments of nuclei of the former Rete-cells. The thickening in question of this layer is not at all frequent; it is at one place greater than at another, and varies also in breadth, extending over a smaller or larger area. In Fig. I. is represented a thickening of this kind, extending, as is seen in the drawing, over a considerable area. I may mention that this is the greatest breadth to which I have seen it extend. The thickening is homogeneous, does not show any distinct traces of nuclei,

but is very conspicuous by its containing minute uniform granules. As we shall have repeatedly occasion to mention hereafter, the abnormal thickenings of the stratum lucidum do not present this granulation everywhere, and even not in all parts of one and the same locality. As long as this granulation is examined in sections made vertically through the thickening, and under a moderately high power, they very much look as if they were minute discontinuities which at some places become confluent into larger or shorter fissures between the corresponding strata. Examining them, however, in a horizontal view and under a high magnifying power, it seems more than probable that we have before us real and veritable granules of a very uniform size. We may dismiss at once the idea that these "granules" are identical with pigment granules, which as is well known may be seen not only in the substance of the hair-shaft, but may be traced also occasionally up to the most superficial layers of Rete Malpighii. Nor can it be said, I think, that the presence of these granules is due to amorphous albuminous matter of some kind or other in a coagulated state; for it is hardly possible to imagine that fluid albuminous matter, *e.g.*, exuded plasm (residues of broken up migratory or other cells must be excluded or account of the very uniform size of the granules), remains in that condition in the midst of a stratum which owes its origin to a confluence, as it were, of the superficial scales of the Rete Malpighii, while these are transformed into horny substance. Thus we arrive at the conclusion that these granules may possibly be masses of micrococci. Here again we have to mention that they do not appear to be stained, a fact which renders their identification as micrococci more difficult. And likewise it is difficult to come to a definite conclusion, for the reason that they do not appear to remain unaffected by caustic potash; the swelling up of the matrix in which they (granules) are embedded renders them invisible.

A similar change may be observed in some of the hair-follicles; in some of these the internal root sheath of the shaft of the hair appears to be much thickened, and to contain over a greater or smaller area the same regular granulation as mentioned above.

The nuclei of the epithelium constituting the external root sheath shows nuclei in the act of division or already divided.

The Rete Malpighii of the epidermis as well as the external root sheath of some hair-follicles contains isolated migrants or small collections of them; they are contained in smaller or larger cavities. In the most superficial parts of the Rete Malpighii are found vesicles filled with fluid or with what appear to be smaller or larger fragments of lymph-corpuscles.

The papillæ of corium are distinct and enlarged, the tissue of the latter contains numerous nuclei, most of them belonging to migratory or lymph cells. The "infiltration" with lymph-cells has its seat also in the tissue surrounding the hair follicles and sebaceous glands, and where the "infiltration" with lymph-cells extends from the depth of the skin into the papillary body of the corium, it extends entirely along the hair follicles and venous vessels.

Among the migrants of the superficial parts of the corium large cells filled with brownish pigment granules, and following chiefly the blood vessels, are very conspicuous.

The sweat glands show considerable changes, the epithelium of the coiled tube being loosened, and in many places detached from the membrana propria; in the lumen are contained in some places particles of disintegrating blood discs.

The deeper parts of the corium and the subcutaneous tissue show the interfascicular lymph-canals very marked, probably due to their being

distended by fluid. The blood vessels are distended by, and filled with blood.

Case 3.—The stratum corneum shows already signs of desquamation, parts of it being loosened, and in the act of separating over smaller or greater areas. There are only traces of thickenings of the stratum lucidum, and in it indications of granulation. The Rete Malpighii is much thickened, the interpapillary processes being long and distinct, so are also the pupillæ themselves. Only a very few isolated lymph-cells may be found in the Rete Malpighii. The intercellular canals are, however, very marked.

The corium of the papillary body is very transparent and shows a considerable amount of infiltration with lymph-cells, some of them pigmented wanderers, these being chiefly distributed along the blood vessels. The blood vessels in the superficial parts of corium distended and filled with blood. Blood is also present around the blood vessels, whence it extends into the interfascicular lymph-spaces.

The sweat glands show the following changes: the nuclei of epithelium in some parts of coiled tube more numerous than in others; the epithelium at some places loosened and even completely detached from membrana propria; a few lymph-corpuscles in the tissue around the coiled tube.

Apparent increase of nuclei of muscles of circular coat of arteries.

Case 4.—Epidermis thickened in both its parts, the stratum corneum showing slight indication of desquamation. In a few places the stratum lucidum is slightly thickened, and contains in these parts a few deeply stained staff-shaped nuclei, the epithelial nuclei, and traces of granulation; a few lymph corpuscles are found in Rete Malpighii.

Intercellular canals, interpapillary processes, and papillæ are in the same condition as in the former case. Likewise the corium is considerably infiltrated with lymph-cells, chiefly along the blood vessels (some of these are quite ensheathed in lymph-cells) and hair follicles.

The sweat glands: at some places an increased number of nuclei of the epithelium of the coiled tube.

The blood vessels are distended and contain blood, amongst which also a certain amount of finely granular matter may be met with.

Case 5.—Stratum corneum thickened, shows indications of desquamation. Rete Malpighii thickened; stratum lucidum shows thickenings, some of which contain staff-shaped nuclei, and also uniform granulations; also these thickenings show signs of desquamation. A few lymph-cells in Rete Malpighii, in the superficial parts of which they are aggregated even to small clusters.

Infiltration with lymph-cells in corium and papillæ chiefly along blood vessels, the nuclei of endothelium of which are distinctly increased; also the nuclei of the epithelium of the external root sheath of hair follicles increased; at the bulb the external root sheath is possessed of a number of longer or shorter digitations composed of small epithelial cells.

The sweat glands show considerable changes: at some places the number of nuclei of epithelium of coiled tubes is increased, at others the epithelium is detached from the membrana propria and fills the tube more or less completely, showing at the same time signs of breaking up into isolated nuclear elements.

The blood vessels are distended by, and filled with, blood, fibrin threads, and numerous colourless corpuscles. The endothelial, as well as muscle, nuclei of arteries appear to be increased in numbers.

Case 6.—Epidermis much thickened, chiefly in the Rete Malpighii. Stratum lucidum slightly thickened at a few places and containing at the same time the remains of the nuclei of the previous epithelial cells. Slight granulation of these thickenings. Papillæ of corium very distinct; their tissue is transparent. A considerable number of nuclei is present in the corium; they are distributed chiefly in connexion with the blood vessels and hair follicles. The nuclei are either oval, large, transparent nuclei of endothelial cells, or deeply stained nuclei of lymph-corpuscles. There are a few migrants in the Rete Malpighii; some of the migrants in the papillary part of corium are pigmented. Pigment is present also at a few places in the deepest stratum of Rete Malpighii.

Blood vessels are distended and filled with blood and fibrin; in the small veins are a good many colourless corpuscles. In the coiled tube of the sweat glands there is no lumen visible, the nuclei of the epithelium in many places in greater numbers than is normally the case.

Case 7.—Epidermis shows no increase; interpapillary processes, however, very distinct and papillæ therefore very marked, long and broad. The stratum lucidum is everywhere well developed, and contains very numerous large granules stained very deeply in hæmatoxylin. The same deeply stained granules are present in the flattened scales of the external root sheath of hair follicles. Pigment present in the deepest cells of Rete Malpighii. Corium contains many nuclei—the nuclei of endothelial cells of blood vessels and nuclei of lymph-corpuscles; the latter are distributed chiefly along the blood vessels and also hair follicles, and to a lesser degree around sebaceous and sweat glands. In the papillæ a few small lumps of pigment; in the corium, in different depths, may be found a few large wandering cells staining extremely deeply in hæmatoxylin. The sweat glands show considerable changes: the nuclei of the epithelium of the ducts distinctly increased in numbers; the epithelium of most parts of the coiled tube completely detached from the membrana propria and more or less broken up, at the same time there is blood more or less unchanged in the coiled tubes.

The blood vessels are distended and filled with blood. In superficial as well as deep parts of corium blood *en masse* is present in some of the perivascular lymphatics. In one instance I have seen an artery surrounded for a considerable distance by a very large space more or less filled with blood, and in another preparation I found the wall of a capillary vessel broken and blood extending along its outer wall for some distance.

The wall of veins and capillaries shows unmistakeably a greater number of (endothelial) nuclei, some of these being constricted or already divided. The interfascicular lymph spaces in the deeper parts of corium and the subcutaneous tissue are very conspicuous.

Case 8.—Epidermis very considerably thickened in all its parts; stratum corneum shows slight signs of desquamation. The stratum lucidum, however, only distinct at the mouth of some large hair follicles, and shows then slight granulation. Rete Malpighii conspicuously thickened, its interpapillary processes long and broad; there is also distinct proliferation of nuclei of the epithelium of external root sheath of hair follicles. In the deeper parts, that is, near the bulb, processes composed of small epithelial cells may be seen in connexion with the external root sheath. Very intensive infiltration with lymph-cells may be observed around the blood vessels of the corium, around the bulbs of hair follicles and sweat glands. Most of them are uninuclear lymph-corpuscles; some contain, however, two or three very small nuclei.

The sweat glands show in many parts of the coiled tube no lumen, this being occupied either by the swollen epithelium or by what appears to me to be a band or cylinder showing a fine and indistinct longitudinal striation, and not dissimilar, therefore, to the so-called fibrin-cylinders in the tubes of the kidney in different forms of nephritis. The distended blood vessels contain blood and matter composed of coarse bright more or less angular particles, which are very similar to those bright particles that one so often sees in various numbers in healthy as well as in diseased blood taken fresh from man as well as from animals.

Case 9.—The chief features of interest are : (*a*), the thickening of the stratum lucidum, which at some places is uniformly granular ; (*b*), the presence of masses of migratory cells at some places in the superficial layers of the Rete Malpighii ; (*c*), the same is the case with the epithelium of the mouth of hair-follicles.

Very slight infiltration with lymph-corpuscles of the superficial parts of the corium ; the blood vessels of corium distended, and contain blood. The epithelium of coiled tubes detached and more or less distinctly breaking up into granular fragments.

Case 10.—Skin not examined.

Case 11.—Epidermis very conspicuously thickened in all its parts. Stratum corneum showing distinct desquamation. The stratum lucidum is in many places, with and without connexion with the mouth of hair-follicles, distinctly thickened and composed of several horny strata still showing the nuclei of the epithelial cells from which they originated. In some parts the thickened stratum lucidum shows granulation. Rete Malpighii very transparent ; distinct signs of germination of nuclei, some of which contain two nucleoli. Some of the nuclei are vacuolated. There is slight infiltration of Rete Malpighii with lymph-cells. Subepithelial tissue, *i.e.*, papillary body, transparent, the papillæ long and distinct ; they contain a very great number of lymph cells, and so does the tissue around the blood vessels of the corium in general. The coiled tubes of the sweat glands show in some parts transparent epithelium and a distinct lumen ; in other parts the lumen is gone, owing to the swelling up of the epithelial cells ; the same applies also to the ducts. Blood vessels in general distended and filled with blood. A few pigmented wanderers may be noticed in the superficial parts of corium.

Case 12.—Stratum corneum thickened ; shows desquamation. The stratum lucidum distinct and slightly thickened at some parts, showing at the same time granulation in some of the thickened parts. In the corium a slight increase of nuclei, chiefly belonging to lymph-corpuscles, may be noticed around blood vessels and hair follicles. The blood vessels are distended, and contain much fibrin, arranged so as to form little tufts of radiating short fibres. Some of the nuclei of muscular coat of arteries appear to be in the state of germination. The nuclei of the epithelium of the coiled tubes of the sweat glands in many instances divided. In some parts the tube does not show any lumen on account of its being filled up by the swollen epithelium.

Case 13. — Epidermis much thickened, especially in the Rete Malpighii. In the most superficial layers of the latter, smaller or larger cavities may be noticed, by which the superficial strata of the epidermis become loosened and more or less completely detached from the Rete Malpighii. These cavities are either small and contain no formed particles, or they are larger and contain then a few droplet-like homogenous structures of very various sizes, probably coagulated plasma. The stratum lucidum is much thickened at some places and distinctly

granular; in some parts of it we can still trace the staff-shaped remains of nuclei of the epithelial cells. Some of the nuclei of the cells of the Rete Malpighii are exceedingly large, and contain also one or two large nucleoli. Intercellular canals very distinct in some parts. Papillæ enlarged. Only few lymph-corpuscles are to be met with in the corium, around the blood vessels, hair follicles, and sweat glands.

Case 14.—Stratum corneum thickened and desquamating. There are only a few places where the stratum lucidum is thickened and granular, it contains also a few staff-shaped nuclei. *Similar thickenings are included in the desquamating stratum corneum, i.e.*, in the superficial strata, which are already more or less separated from the surface of the Rete Malpighii.

Only very few lymph-corpuscles are to be met with in the Rete Malpighii. Pigmentation at some places of the deepest stratum of epithelium.

Papillæ of corium very distinct and long.

Directly underneath the epidermis the corium is very transparent.

The tissue of the corium shows infiltration with lymph-corpuscles chiefly around the blood vessels and the root of hair-follicles. In the apex of some papillæ are found occasionally homogeneous highly refractive drop-like masses. It cannot be determined whether these are derivatives of blood contained in vessels. I may mention here that similar masses I have repeatedly noticed in the same places and also, as it seems to me, in the epidermis in several other cases.

The ducts and coiled tubes of sweat gland show in some parts more numerous nuclei of epithelium than in others.

The lumen is not visible everywhere as the epithelium seems to fill up the tube.

The bulb of hair follicles shows the processes of the external root sheath so repeatedly mentioned.

The blood vessels of deeper parts of corium contain blood and fibrin; very marked proliferation of the nuclei of muscle fibres in the coat of arteries.

Case 15.—Skin not examined.

Case 16.—Epidermis shows considerable desquamation of thickened stratum corneum. The stratum lucidum thickened in many parts, granular, and contains particles which stain deeply in hæmatoxylin—remains of nuclei. Similar masses are included in the desquamating layers of the stratum corneum. The same condition is to be observed on some large hair follicles, the hair of which is surrounded near the mouth of the follicle by an exceedingly thickened, granular, internal root sheath; immediately around the hair are closely aggregated deeply stained particles—remains of nuclei—and in some instances the whole surface of the hair is of a uniform deep blue tint in preparations that had been stained in hæmatoxylin. The Rete Malpighii is much thickened. The papillæ of corium very distinct. Infiltration with lymph-cells chiefly around blood vessels and around the root of hair follicles. The arrectores pilorum are exceedingly well developed; there are signs of germination of the nuclei of the muscle fibres.

Blood vessels are distended and contain blood and coarse highly refractive particles, and also little tufts of radiating short fibrin-fibres.

Sweat glands show slight change; in some parts of the coiled tube the epithelium is very transparent and is filling up the tube so that no lumen can be detected.

Case 17.—Desquamation of stratum corneum. The Rete Malpighii is not perceptibly thickened. Pigmented lumps are present in the

deepest epithelial cells external to the nucleus. Corium is only very slightly infiltrated with lymph-corpuscles around blood vessels, hair follicles, and sweat glands. Distinct increase of nuclei of the endothelium of small veins. The blood vessels of the deeper parts of corium are distended and contain blood corpuscles and small irregular highly refractive granules. The epithelium of coiled tubes of sweat glands in some parts swollen so as to fill up the lumen, in others it is breaking up.

Case 18.—Epidermis very much thickened; stratum corneum desquamating. The stratum lucidum distinctly thickened and in many places uniformly granular; similar uniformly granular masses slightly stained with hæmatoxylin are to be met with in the desquamating parts.

The uniformity of the granules forming smaller or larger lumps is very characteristic of micrococci, and the aspect such, that although one cannot fully express its peculiarity in describing it, one can hardly fail to perceive it under the microscope, whatever their chemical character may be.

In Fig. III. I have represented these appearances, and it cannot be denied that the resemblance between lumps of micrococci and the masses in question is very great. More than this I do not venture to say.

Rete Malpighii much increased in thickness. Papillæ of corium enlarged. The superficial parts of the corium are very much infiltrated with lymph-corpuscles, most of these possess two or three small nuclei. The infiltration with lymph-corpuscles is greatest around blood vessels and hair follicles, to a lesser degree around the ducts of sweat glands. Pigmented wanderers are to be met with in the papillary tissue; pigment is present also in the deepest stratum of the Rete Malpighii.

The lymph-canal system of deeper parts of corium very distinct.

In many parts of the coiled tubes of the sweat glands the epithelium is transparent, filling up the tube, in other parts the epithelium is breaking up into granular masses.

Case 19.—Desquamation of layers of thickened stratum corneum. The stratum lucidum is thickened at some places and granular. Similar masses (containing in addition also a few remnants of nuclei) are contained in the desquamating layers of the stratum corneum.

Some of the large hair follicles show the analogous changes, consisting in a thickening of the internal root sheath, which includes remnants of nuclei of epithelial scales, and in many parts also the uniform granulation. Figs. IV. and V. are drawn from preparations obtained of this case.

The Rete Malpighii increased in thickness; many nuclei in state of division; some of the nuclei of the deeper and superficial layers are vacuolated, or shrunk and folded or crescentic. These appearances are to be met with also in specimens of several other cases, but there does not seem to be any regularity in the occurrence of these phenomena.

The papillæ of corium distinct. Much infiltration in the corium with lymph-cells, chiefly around veins and hair follicles.

There is a very conspicuous increase of the nuclei of the endothelium of the smaller veins, many of the nuclei showing at the same time a longitudinal linear mark.

The nuclei of the muscle fibres of the arteries show likewise signs of germination. A similar appearance is presented by some of the nuclei of the arrector pili. The sweat glands are filled up in most part with their epithelium, which in some portions of the coiled tube is detached and even breaking up.

Case 20.—Desquamation of the thickened stratum corneum. Rete Malpighii not conspicuously thickened, on the contrary at some places it is decidedly thinner than normal. In the neck and mouth of hair follicles the internal root sheath is much thickened, granular, and includes even a few deeply stained remnants of nuclei. The external root sheath of the deeper parts of hair follicles is possessed of smaller or larger processes composed of small epithelial cells.

The papillæ of corium distinct and transparent.

The tissue of corium shows slight infiltration with lymph-cells chiefly around blood vessels, hair follicles, and sebaceous glands. The arrectores pilorum very well developed. Distinct lymph spaces around their constituent bundles. The sweat glands show a great number of nuclei; in many parts of the coiled tubes the epithelium is swollen, transparent, and is completely filling the lumen of the tube.

Blood vessels distended, contain blood, fibrin, and granular matter.

Case 21.—Desquamation so intense that at some parts the stratum corneum is altogether gone. The stratum lucidum is thickened at some places more than at others and granular; it contains also occasionally a few staff-shaped nuclei stained deeply in hæmatoxylin. The subepithelial tissue is loose and very transparent. The tissue of corium very slightly infiltrated with lymph-cells, chiefly along the blood vessels (small veins) and hair follicles, and to a slight extent also around sweat glands. Pigmented wanderers are to be met with in the superficial parts of corium; pigmentation also observable in the deepest epithelial stratum.

In some parts of the sweat glands the nuclei of epithelium are more numerous than in others, the epithelial cells at some places almost filling up the coiled tubes. The blood vessels are distended, the deep ones filled with blood, amongst which a few fibrin threads may be detected. Interfascicular lymph-spaces of deep corium and subcutaneous tissue very distinct.

Case 22.—Skin not examined.

Case 23.—Thickened stratum corneum, and also thickened Rete Malpighii. The stratum lucidum is distinct at some places and contains a few brownish pigment granules.

Papillæ of corium distinct. The blood vessels all through the corium are very distended and filled with blood; considerable masses of fibrin in them. In the wall of blood vessels numerous nuclei, amounting at some places to small collections of lymph-corpuscles. A few pigmented wanderers in the papillary tissue.

The sweat glands show little change; in some parts of the coiled tube the epithelium is swollen and filling up the lumen; the capillary blood vessels around the coiled tubes distended and therefore very distinct.

In connexion with the external root sheath of hair follicles are cylindrical processes composed of small epithelial cells.

B.—*General Remarks on the Anatomical Changes of the Skin in Scarlatina.*

From the foregoing it is evident that the descriptions of the microscopic appearances of the eruption, generally given in text books, require additions in several respects. The changes of the skin in the eruption are represented to be those of hyperæmia and inflammatory œdema, more or less well marked in the superficial layers of the skin.

Löschner* speaks of an exudation into the Rete Malpighii containing fluid and formed parts, *i.e.*, cells of various shapes and sizes.

We have in several cases mentioned the presence of lymph-cells in the Rete Malpighii; in fact it appears to be the rule that in the earlier stages migratory cells find their way from the papillæ into the Rete Malpighii, where they may be found isolated or in smaller or larger groups in corresponding cavities. We have likewise called attention to the irrigation of the Rete Malpighii with abnormal quantities of fluid, *i.e.*, plasma, as is evinced by the formation of cavities and the collection of fluid in them in the upper part of the Rete Malpighii, and the great distinctness, *i.e.*, distension, of the intercellular canals.

In addition to this we have noticed in the eruption of almost all stages the increased thickness of the epidermis, and the enlargement of the interpapillary processes; in the Rete Malpighii we have seen distinct signs of division of nuclei and nucleoli (enlarged nuclei, constricted and double nucleoli), thus making it probable that the increased thickness of the Rete Malpighii is due to a multiplication by division of the cells of the Rete Malpighii. In the late cases, however, the Rete Malpighii is found not to be so much thickened. Before the desquamation of the epidermis becomes perceptible in the living subject by clinical observations, the microscope, as we have seen, reveals two important facts: (*a.*) the local thickenings of the stratum lucidum; and (*b.*) the loosening and even detachment of smaller portions of the superficial parts of the epidermis. Those thickenings which indicate a rapid conversion of portions of the superficial strata of the Rete Malpighii into horny masses contain masses of minute granules, the character of which, whether micrococci or not, cannot at present be definitely ascertained. Nor can the nature of similar granules be determined which are filling the cavities in the epidermis of that very early case that had been examined, viz., Case 1, that died after two days' illness.

Similar changes as in the Rete Malpighii have been noticed in the hair follicles, *i.e.*, distinct germination of the epithelium of the external root sheath, and occasionally also a few migrants amongst its cells; further, thickening of the internal root sheath (which evidently corresponds to the stratum lucidum of the epidermis), and also the presence of nuclei, or parts of nuclei, being the nuclei of the cells out of which this structure is being formed, and masses of granules.

Fenwick† found in three cases the Rete mucosum thickened, and containing numerous round cells with large nuclei; and further he mentions that the epithelium of sweat glands becomes thickened so as to fill the tube; it then becomes detached and removed from the basement membrane, which is thickened. In one of the cases the coiled tubes were loaded with coagulated blood; in another case the external layers of the cuticle were stained with blood in patches, and the ducts of the sweat glands were also reddened. As I have repeatedly mentioned, there was in many early cases germination of the epithelium in the coiled tubes as well as in the ducts, and likewise partial detachment and even breaking down of the lining epithelium; but I cannot quite see how these appearances are placed side by side with the desquamation of the epidermis, as is done by Fenwick. This author believes that inasmuch as the epithelium of the sweat glands becomes first thickened and then detached from the basement membrane, the changes in the sweat

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* Quoted in Thomas's Article, l.c., p. 211.

† The Morbid States of the Stomach and Duodenum. 1868, p. 107.

glands are analogous to those of the epidermis. This opinion is, to my mind, based on a misconception of the nature of the desquamation of the epidermis. The difference between the two processes is very obvious. In the epidermis we find a very active new growth, and then a very rapid and copious horny transformation and subsequent detachment of the strata so changed; in the sweat glands, on the other hand, it is true we meet at nearly all stages of the disease, in some parts of the glands, a multiplication of the nuclei of the epithelial cells, and even an enlargement of these latter, so as to fill up the tube completely, but whether in consequence of active growth, or of swelling up due to the inflammatory exudation, I do not pretend to know, but then there is detachment of epithelium from the basement membrane and a total breaking down of the former. It seems to me that this detachment of the epithelium in some parts of the tube is in no way connected with or subsequent to the enlargement of the epithelium, for both occur side by side and both are caused by the inflammatory conditions. Why should the detachment of the epithelium from the basement membrane and the subsequent breaking up not be caused by an excessive exudation of fluid from the blood vessels, just in the same way as in other parts of the body excessive exudation of fluid produces a loosening and disintegration of epithelium, *e.g.*, that of the surface of mucous membranes in inflammation?

I cannot state with confidence the thickening of the membrana propria of sweat glands, which is mentioned by Fenwick in his cases.

Among the 20 cases only in one case (case 7, death after five days) have I observed blood more or less altered in sweat glands. In this case there were masses of blood in lymph-spaces which (blood) had escaped from ruptured blood vessels.

Thomas, l.c., says on p. 210, "Under the influence of a hæmorrhagic "diathesis, which may be superinduced by a severe scarlatinous affec- "tion, especially under otherwise unfavourable circumstances, exuda- "tions of blood often take place into the superficial layers of the skin " . . . . . hæmorrhages into the subcutaneous cellular tissue may also "occur."

If the changes of any part of the eruption are to be regarded as analogous with those of the epidermis, it is those of some of the hair follicles, in which we have seen not only very distinct signs of active germination of epithelium, but also copious formation of horny masses in form of what appears to be thickened internal root sheath.

I pass by without special comment the general inflammatory condition of the corium in the earlier stages, *i.e.*, enlarged papillæ, increased irrigation with fluid, viz., distended interfascicular lymph-spaces, distended blood vessels, and the infiltration with lymphoid cells. With reference to these latter I have specially to mention their distribution, they being chiefly contained in the tissue around blood vessels—veins and capillaries—hair follicles, and in some cases also around sweat glands.

Of greater importance is the change we have observed in the walls of blood vessels; this consists, in (*a*), a distinct germination of the nuclei of the endothelium, and (*b*) of the nuclei of the muscle-cells in the coat of arteries. Around some of the blood vessels may be found numerous oblong nuclei of the general character of endothelial nuclei, and hence it is probable that a multiplication takes place also of the nuclei of the endothelium of perivascular lymphatics.

III.—Microscopic Examination of Kidney.

(A.)—*In the above Cases.*

Case 1.—The examination of this case, which, as may be remembered, was the earliest of the series, proved of great importance, as the tissue of the kidney presented already certain important changes. These changes are limited chiefly to the cortical substance. Near the capsule many Malpighian capsules are met with which are filled with granular matter and blood; the same material is contained also in the convoluted tubes. Many of the glomeruli show a much greater number of nuclei than in the normal condition. On more careful examination it is found that the increase of nuclei is due to a germination of the nuclei of the epithelial cells attached to the external surface of the capillaries, and most probably also to a germination of the nuclei of the wall of the capillary vessel itself. The epithelium lining Bowman's capsule is in some Malpighian corpuscles composed of large, almost columnar, opaque cells, the nuclei of which are in a state of division or already divided. The most internal part of the cortex, *i.e.*, that bordering on the basis of the pyramids, contains few Malpighian corpuscles, in which little only of the glomerulus is to be detected (see Figs. XI.), the interior space of the Malpighian corpuscle being much smaller in size, owing to the presence of concentric more or less distinctly fibrous layers, which apparently belong to Bowman's capsule; in them may be recognised round or oblong nuclei. I have followed these changes in many Malpighian corpuscles, and I have come to the conclusion that the nuclei of these fibrous more or less concentric layers are the nuclei of the epithelial cells as well as of the capsule, which cells have apparently undergone fibrous degeneration. The material in question does not look everywhere like fibrous tissue, for in some instances it presents more the appearance of a homogeneous substance which is indistinctly striated. In some Malpighian corpuscles this degeneration shows itself as a thickening of the capsule, whence the degeneration seems to spread on to the glomerulus, attacking first one lobule and then another. The degenerated parts become fused so as to form one continuous mass. During all this time the nuclei of the glomerulus itself become very much increased in number, many of them showing distinct signs of division; the wall of capillaries swells up and the lumen gradually disappears. In a further advanced stage nothing is left of them except a few opaque masses containing groups of nuclei. The amount of fibrous tissue containing a few nuclei around the so changed Malpighian corpuscle is considerable. It is very peculiar that these changes should be found on Malpighian corpuscles situated in the most internal portion of the cortex. I may mention on this occasion the presence of groups of lymph-cells, with one or two or three small nuclei in the tissue around the large arterial trunks penetrating between cortex and pyramids.

[There are bundles of unstriped muscle fibres of considerable thickness in the tissue around the arterial trunks, and also in the tissue of pelvis. The nuclei of this muscular tissue show the same proliferation as in the arteries.]

Another important change is to be found in the cortical arteries, the larger branches as well as minute arterioles. This change consists in a very active division of the nuclei of the unstriped muscle fibres; in many instances the characteristic staff-shaped nuclei are replaced by a linear series of two, three, four, or more small nuclei. There can be no doubt that these result from the division of the original staff-shaped nuclei. In many instances, especially in the small arterioles of the cortex, the muscular coat is in consequence of these changes thicker than in the normal condition. Besides the germination of the nuclei of

the muscle fibres, also the nuclei of the endothelium of the arterioles undergo multiplication. To these facts must be ascribed the peculiar appearance that presents itself at the peduncle of some Malpighian corpuscles, for there we find a very conspicuous number of nuclei, which can be still recognised as having resulted from division, both of the longitudinal nuclei of the endothelium and the transverse nuclei of the muscular fibres. Another noteworthy appearance in connexion with this change in the afferent and efferent arterioles is the great abundance of nuclei in the epithelial lining of what appears to be an ascending tube of Henle, and what is still more peculiar is that, this increase of nuclei is generally to be observed only on that part of the wall of the tube which is in contact with, or nearest to, the afferent arteriole. I have represented these changes in Fig. VI., accurately copied from a preparation.

Besides the changes enumerated, there is some other change to be noticed on afferent arterioles, either close to the Malpighian corpuscle, or after having already penetrated through the capsule, consisting in the swelling up of a portion of the intima, or a greater or smaller part of the circumference of the arteriole into a hyaline, highly refractive material, resembling what is described by some pathologists as glassy hyaline degeneration; it does not yield amyloid reaction. (I have represented these appearances in Fig. VII.)

It becomes thus probable that the degenerative changes of the Malpighian corpuscles above described are analogous to these changes of the arterioles. The degeneration of Malpighian corpuscles is not of the nature of amyloid degeneration as has been already evident from our description. Iodine, as well as methylaniline, which has come into use only recently for demonstrating amyloid substances, gives no reaction. (We shall learn more about the nature of this degenerative process in some of the following cases, where it is more easily followed.)

With reference to the urinary tubes, there are certain changes to be observed; they are: cloudy swelling of the epithelium of a few convoluted tubes, which leads to disintegration of the epithelial cells; in others the nuclei are double in some of the epithelial cells.

In the cortical as well as in the medullary portion of the ascending tubes of Henle, the epithelial lining is in some instances detached from the membrana propria, and in addition to this, in the cortex, breaking up into small nuclear fragments. There are a few hyaline cylinders to be met with in Henle's loops.

Some of the large collecting tubes of the pyramids are collapsed. Their epithelial lining is shrunk into an opaque mass; in others the epithelial lining is altogether gone.

In this, as well as in most other kidneys, I found a considerable quantity of yellowish brown pigment in the form of smaller or larger granules or irregular lumps contained in the epithelial lining of the descending limb of Henle's loops just as they emerge from the cortex, and it may be traced in them for a little distance into pyramids. The extent in which pigment is found in the epithelium of these tubes varies in different kidneys, but at all events it seems to form as a part of the normal structure of the kidney. (This pigment will be mentioned hereafter only where it occurs in large quantities.)

Case 2.—The changes in this case are similar to those in the preceding one, only not so intensive, as there are no Malpighian corpuscles which have become degenerated in the manner above mentioned. In one instance only have I seen a Malpighian corpuscle near the pyramids which showed degeneration of the glomerulus.

Many Malpighian corpuscles, however, show an increase of the nuclei

of the glomerulus: signs of division of nuclei, and even nuclei already divided are not rare. Also the swelling of the epithelial cells (and division of their nuclei) of the capsule near the neck of the convoluted tube may be met with. The cavity of some Malpighian corpuscles contains granular matter and what appears to be remnants of blood corpuscles. Granular material is also contained in the convoluted tubes. The germination of the nuclei of the muscular coat, and also of the endothelium of arterioles, as described in the former case, may be observed also here; and likewise the great increase of nuclei of the epithelial lining of that part of an ascending Henle's tube which is in contact with the afferent arteriole next the Malpighian corpuscle. In some glomeruli next the pyramids the wall of capillary vessels is thickened and swollen. In the close vicinity of a large arterial trunks I have found a Malpighian corpuscle, around which there is a collection of lymphoid cells, with one, two, or three nuclei.

The epithelial lining in a few convoluted tubes shows cloudy swelling; in some epithelial cells the nucleus is very small, faintly stained as if disappearing--or perhaps in the course of formation—in others the nucleus is double. In a few convoluted tubes the swollen epithelial lining is disintegrating and breaking up into granular fragments. Many of the ascending Henle's tubes in the cortex show their epithelium detached and disintegrating.

The collecting tubes of the pyramidal portion show in some instances their epithelial lining detached and breaking up into small nuclear fragments, or even entirely gone. In the latter case the membrana propria is seen to contain large nuclei, either isolated or in groups of two or three, and the impression is produced as if it were composed of endothelial plates. Near the papilla cylindrical or irregular masses may be found composed of coarsely granular amorphous or globous matter, which in unstained preparations have the same shining aspect as amyloid; they do not show, however, the chemical reactions characteristic of amyloid; and assume a more or less deep purple-violet colour in hæmatoxylin. They appear to be contained in tubes—apparently collecting tubes—which are distended and blocked up by them occasionally to such an extent that the surrounding tissue is more or less degenerated. The material in question is soluble in dilute hydrochloric acid without, however, effervescing; it is therefore not carbonate of lime but probably some other salt of lime.

There are also a few hyaline cylinders in collecting tubes of the pyramids.

In the tissue of the calices are found numerous mono-nuclear lymph-corpuscles, some of which are conspicuous by their size, their deep staining, and their coarse granulation.

Much pigment is present in the first part of the descending limbs of Henle's loops.

The larger blood vessels are filled with blood. Numerous colourless blood corpuscles and also a little fibrin in veins.

Case 3.—The glomeruli show in most instances an increase of the number of nuclei; in some the wall of the capillary vessels appears swollen, more or less degenerated into a granular or slightly fibrillar mass. The internal portion of the cortex contains Malpighian corpuscles in which degeneration has advanced considerably on the capsule as well as the glomerulus. The cavity of many Malpighian corpuscles contains granular matter, disintegrated cells, and what appear to be the remains of blood discs. In one instance the glomerulus was quite collapsed and in its stead a heap of nuclei was to be found, whereas

the cavity of Bowman's capsule was filled with a uniformly and finely granular substance slightly stained in hæmatoxylin in which were embedded a few lymph-corpuscles. At a peripheral point in the same Malpighian corpuscle was found a lump of the same globular matter (lime) of deep purple colour as has been mentioned to occur in tubes of the papilla in the previous case. In the smaller as well as in the larger arteries, there is the same germination of the nuclei of the muscular tissue, in the former also of the nuclei of the endothelium. Likewise we meet with the increased number of nuclei of epithelial cells in that part at the ascending Henle's tube next an afferent arteriole, as has been mentioned in the preceding cases. The hyaline swelling of portions of the intima of afferent arterioles before and after having penetrated Bowman's capsule is conspicuous. In the connective tissue surrounding the large vascular trunks, penetrating between cortex and pyramids, may be noticed numerous lymph-cells, amounting at some places to considerable collections. They extend into the cortex as well as (although to a smaller extent) into the pyramids for a short distance ; in the former they are situated between the convoluted tubes and around the adjacent Malpighian corpuscles, in the latter they extend between the straight blood vessels and urinary tubes.

The epithelium of a few convoluted tubes shows cloudy swelling; in some the epithelium is filled with small vacuoles or even disintegrating into granular fragments ; the latter condition may be met with chiefly in the first part of the convoluted tubes, *i.e.*, that next Bowman's capsule. In many of the swollen epithelial cells of convoluted tubes a germination of nuclei may be noticed. Some of the tubes of Henle and also some of the collecting tubes contain cylinders composed of hyaline or more or less granular material.

The same irregular masses of granular or amorphous globous (lime) matter observed in the papillary part of the preceding case may be found in this case. Here also they stain deeply in hæmatoxylin.

The larger blood vessels are filled with blood ; the veins contain numerous colourless blood corpuscles and fibrinous matter.

On the naked-eye examination of the kidney of this case no trace is to be perceived of the extensive changes described in the foregoing.

Case 4.—Many Malpighian corpuscles contain granular matter and remains of blood. The same is the case in the distended convoluted tubes. The epithelium of some of the latter is either detached from the membrana propria or is in the state of cloudy swelling, or disintegrating into fragments of granular matter.

The germination of the nuclei of the endothelium, but chiefly of those of the muscular coat of arterioles, is very distinct, and especially remarkable is the number of nuclei (nuclei of muscle fibres and of endothelium) of arterioles just at the point of entering Bowman's capsule.

Besides these changes also the hyaline swelling of portions of the intima may be observed in some arterioles. The Malpighian corpuscles whose glomerulus is in a state of fibrous degeneration are very scarce, and then they are near the periphery and of an "embryonic character."

This last expression requires some explanation. In kidneys of young subjects, such as those whose bodies were the source of our anatomical material, there are found in the peripheral part of the cortex small Malpighian corpuscles (their number is always limited, and is smaller in older children than in infants), which differ from ordinary Malpighian corpuscles in the following respects : (*a*) they are very small and only few or no distinct

capillary vessels are to be observed in them, (*b*) the glomerulus is covered with a continuous layer of polyhedral epithelial cells. It is evident that these Malpighian corpuscles are not yet fully developed, but possess still an embryonic character. I have observed in this and in other cases of scarlatina that the "embryonic" Malpighian corpuscles are very favourite subjects of fibrous degeneration.

Many glomeruli show an increased number of nuclei, and the wall of the capillary vessels is opaque and thickened.

The epithelium of ascending tubes of Henle in the periphery of cortex is detached from the membrana propria, or is even breaking up into small elements.

Arteries and veins are full of blood, also a slight amount of fibrin may be noticed in them.

In veins of pyramidal portion numerous colourless blood corpuscles.

Whenever we do not make any special mention of the condition of the intertubular capillary blood vessels of the cortex it will be understood that they are not visible in our hardened specimens.

Arteries as well as veins contain a few cylindrical or spherical more or less homogeneous lumps of a glistening aspect; they look very much like soft gelatinous casts of capillary vessels. They possess, it is true, the peculiar glistening aspect of fat, but they do not show any chemical reaction characteristic for fat; they are most probably derivations of blood.

Small accumulations of lymph-corpuscles may be met with in the adventitia of a few interlobular arteries as well as veins.

Case 5.—This case may serve as a further illustration of the fact that although on superficial examination there is little change to be noticed, the careful examination of well-stained (hæmatoxylin) sections reveals considerable progress in the vascular alterations. These are as follows: (*a*) in many glomeruli the number of nuclei increased; (*b*) arterioles show the hyaline swelling of intima, *i.e.*, blocks of colloid-looking matter in this latter, in a few cases leading up to total obliteration and degeneration of the vessel; the swollen-up wall looks then more like a fibrous material. This hyaline swelling is present also in a greater or smaller number of capillaries of glomeruli, their wall containing an oblong or spherical block of that hyaline substance. In glomeruli of this kind the wall of the capillaries in general is of a granular and opaque aspect.

Near the capsule of the kidney are a few "embryonic" Malpighian corpuscles, in one or the other portion of which fibrous degeneration has already commenced.

The arterioles in general, even where their lumen is not to be seen, are recognisable by the great number of nuclei of the endothelium, but chiefly of the muscular coat. The germination of nuclei of the epithelium of that portion of Henle's tube next an afferent arteriole is also here conspicuous.

The connective tissue, in which are embedded the large vessels, contains small collections of lymph-corpuscles.

Some Malpighian corpuscles contain granular matter and blood, so also the convoluted tubes near the capsule of the kidney, and to a smaller extent the convoluted tubes in the inner part of cortex. In a few of the latter the epithelium shows cloudy swelling, fatty degeneration, and even disintegration.

In other convoluted tubes the nuclei of epithelial cells are proliferating. The epithelium of ascending Henle's tubes near the capsule

of the kidney is detached from the membrana propria, and even breaking down into small nuclear granular elements.

A similar condition, though to a lesser degree, may be observed in some of the ascending branches of Henle's loops in the pyramids, and also in some of the large collecting tubes of the latter region.

Considerable amount of pigment in the first part of descending branch of Henle's loops.

There are a few hyaline cylinders in tubes of cortex as well as pyramids.

Case 6.—This case is *in every respect* similar to the preceding one, especially with reference to the changes in arterioles and glomeruli. The germination of nuclei of muscular coat is distinctly perceptible, also in the large arterial trunks; in the latter the muscular coat is markedly thickened. Thus I find in a branch of the renal artery filled with blood, the whole diameter of which branch (including the adventitia) amounts to very little over 0·7 mm., the muscular coat at some places measuring over 0·2 mm. In the same branch there was present at one point an internal longitudinal muscular layer of about 0·05 mm. thickness.

Also the urinary tubes show the same changes as in the preceding case. Much granular matter and fat droplets in the convoluted tubes. There is infiltration with lymph corpuscles of the connective tissue of calices, extending into the connective tissue around the interlobular vessels, and hence between the urinary tubes and Malpighian corpuscles of the adjoining parts.

In the urinary tubes of the basis of pyramids a few hyaline cylinders.

Case 7.—The changes of this case are similar to those of case 5, with the following additional features: (*a*) there are a few Malpighian corpuscles near the capsule of the kidney (which is much thickened, and which contains just at this point a few bundles of unstriped muscles) filled with a very finely and uniformly granular material which had stained with hæmatoxylin; in it were included a few lymph-corpuscles; (*b*) between tubes of cortex a few of those amorphous (lime) masses stained very deeply in hæmatoxylin; (*c*) the epithelium of some urinary tubes of cortex, collecting tubes, and chiefly Henle's ascending tubes, is breaking up into small fragments. The epithelium of many convoluted tubes is also disintegrating. There is considerable amount of pigment.

[The preparations of this case have not stained well with hæmatoxylin, the tissue assuming a uniform dirty violet-brown colour, although the staining fluid itself was of the usual quality.]

Case 8.—As far as the amount of change is concerned, the kidney of this case is nearly as early as any that I have examined; the changes are as follows: (*a*) thickening of minute arterioles due to germination of nuclei of endothelium, but chiefly of those of the muscular coat; the great number of nuclei is especially conspicuous in the arterioles entering Bowman's capsule. (*b*) A few embryonic Malpighian corpuscles in the state of degeneration. I have seen a Malpighian corpuscle near the internal margin of cortex, the glomerulus of which was almost completely transformed into a group of swollen hyaline, or very faintly fibrillar lumps, and between them a few nuclei; the tissue around this Malpighian corpuscle was infiltrated with lymph-corpuscles, extending also between the urinary tubes of the immediate vicinity. (*c*) In the adventitia of some of the large vascular trunks small collection of lymph-corpuscles may be noticed. (*d*) The nuclei of many glomeruli increased in numbers. (*e*) The Malpighian corpuscles contain granular matter and

remnants of blood (viz., decolourized blood discs); the same material is contained in the convoluted tubes near the base of pyramids, *i.e.* the first, section of the urinary tubes; epithelium of some convoluted tubes swollen; numerous cells possess two nuclei; in some convoluted tubes the epithelium appears to become disintegrated. (*f*) Epithelium in many ascending branches of Henle's loops, and also in collecting tubes of pyramids, detached from membrana propria.

There are a few hyaline cylinders in tubes of pyramids. Blood vessels next the capsule in some parts distended and filled with blood. Large veins as well as arteries filled with blood, granular matter, and fibrin.

Bundles of unstriped muscle fibres may be found in the tissue surrounding the larger vascular trunks. Also in this kidney I found a large branch of the renal artery that possesses at one part a longitudinal bundle of unstriped muscle fibres internal to the circular muscular coat.

Some veins contain numerous colourless blood corpuscles.

Case 9.—A few obliterated Malpighian corpuscles. Many Malpighian corpuscles show abundance of nuclei. In some the capillary vessels are very opaque. Slight infiltration with lymph-cells of the tissue around large vascular trunks, which extends also on the tissue around some interlobular arteries and Malpighian corpuscles. Granular disintegration of epithelium of some convoluted tubes. (The epithelial cells lining the first part of convoluted tubes, and also that of the ascending branches of Henle's tubes of cortex, show very well marked the well-known rods first described by Heidenhain.)

The blood vessels of the fresh kidney had been injected with $\frac{3}{4}$ per cent. saline solution, then with Berlin-blue, and hardened in a mixture of chromic acid and spirit.

In many urinary tubes of the cortex the epithelium appears loose or entirely detached from the membrana propria. Near the capsule of the kidney the epithelium of urinary tubes (convoluted tubes and ascending Henle's tubes) is breaking up into small nuclear granular fragments.

In the pyramids the epithelium of many ascending branches of Henle's loops, and also of collecting tubes, is detached from the membrana propria. In the latter it may be found even breaking up into the individual cells.

Many Malpighian corpuscles of the periphery of cortex contain granular matter and what appears as decolourised blood corpuscles, or parts of them. There are a few hyaline or finely granular pigmented cylinders in tubes of cortex.

The kidney was swollen and hyperæmic. In some of the calices was contained an amorphous brittle mass which yielded no reaction with acids, ether, or alcohol.

Case 10.—The following are the predominant changes: (*a.*) Increase of nuclei in many glomeruli. The wall of capillary vessels appears at the same time much thickened, or replaced by opaque, granular, or slightly fibrillar matter. Of this last substance, *i.e.*, fibrillar substance, I am not quite certain that it is not between the capillary vessels. There are also Malpighian corpuscles that have become quite degenerated. The germination of nuclei of muscle fibres of afferent arterioles is very marked just before this latter enters the Malpighian corpuscle. At the same place is also conspicuous the number of nuclei of the epithelium of the Henle's tube lying close to the arteriole. (*b.*) There are numerous arteries in the different parts of cortex, especially those next the large trunks, the intima of which has over a larger or smaller

area, swollen up into a homogeneous glistening substance, which in some places is so large that it narrows the lumen of the vessel to a considerable extent. I have seen an arteriole where this thickening is present only on one side of the vessel, and it is of so high a degree that the lumen has become excentrical and reduced to a minimum size. In arterioles in which the intima has changed only slightly, the nuclei of the muscular coat are seen in a state of division; where, however, the intima has considerably swollen up the muscular coat seems to have given way altogether. Some of the larger arterial trunks and also some of the interlobular arteries contain lymph-corpuscles in their adventitia.

At some places the connective-tissue of calices is much infiltrated with lymph-corpuscles, which infiltration extends on to the tissue around the large veins.

Many Malpighian corpuscles contain granular matter and remnants of blood. There is a considerable amount of granular matter in convoluted tubes, many of which are changed; either their epithelium is slightly swollen and the nuclei of the latter abnormally numerous—in some of the swollen epithelial cells are contained as many as seven or eight nuclei—or the epithelial cells are full of minute vacuoles and disintegrating into granular fragments, the nuclei having previously disappeared; or, finally, the swollen epithelial cells are filled with fat droplets.

A few hyaline cylinders, including coarse granules, may be found in Henle's tubes of cortex. Also a few of those deeply stained amorphous or globose (lime) masses are found in the cortex. There are a few hyaline cylinders in the pyramids, some including yellowish granules in their central part. The epithelium of ascending branches of Henle's loops, and also of collecting tubes of pyramids, is in many instances detached from the membrana propria, and breaking up into small elements; in the former some parts of the epithelial cells show the rod-like structures of Heidenhain with great distinctness. [This is to be noticed also in many of the other cases.] In the large collecting tubes of the papillary portion the lining epithelial cells are very transparent, some of them becoming disintegrated.

The large blood vessels, veins as well as arteries, are filled with blood.

Case 11.—There are a few large arterial trunks the tissue around which is more or less filled with lymph-corpuscles, chiefly small cells containing two or three small nuclei. These cells extend between the convoluted tubes; some of the latter are quite filled with them. Some Malpighian corpuscles contain granular matter and what appears to be remnants of blood. The same is contained in convoluted tubes, especially in the periphery of cortex.

There are a few places at the basis of pyramids where lymph-corpuscles are found accumulated in the tissue around some of the large vascular trunks.

Blood vessels next the capsule filled with blood. The blood vessels of the basis of pyramids distended, and contain more or less altered blood. There are a few hyaline cylinders in tubes of the last-named region. The epithelium of the collecting tubes of pyramids is normal.

Case 12.—Many glomeruli show an increased number of nuclei; some of these appear imbedded in granular opaque cell-substance, the wall of the capillary vessels being at the same time less distinct. From Malpighian corpuscles of this condition there are intermediate conditions to Malpighian corpuscles which show no distinct capillary vessels, but which are occupied by hyaline or slightly fibrillar masses in and between which nuclei are still to be recognised. In Fig. XII. is repre-

sented a Malpighian corpuscle which shows a thickened degenerated capsule, a part of the glomerulus is converted into a hyaline or slightly fibrillar material; other parts are represented by nuclear opaque cell-masses. From the examination of this and other cases, I have become convinced that the obliteration of Malpighian corpuscles, *i.e.*, their conversion into fibrous masses, starts with an increase of the nuclei of the glomerulus, is then followed by the appearance of large granular or hyaline masses, including those nuclei, the capillary vessels at the same time becoming less distinct; after this the capillary vessels become altogether invisible, whereas those masses gradually change into a more or less fibrillar structure, in which nuclei remain visible for some time. The capsule of the Malpighian corpuscle has become thickened during this time—generally this is already perceptible at the outset—its layers swell up first into a hyaline mass in which the nuclei of the original epithelium may be recognised, and gradually become converted into a fibrillar substance.

In the case we have now under consideration there are Malpighian corpuscles next the large vascular trunks, as well as some of the peripheral embryonic Malpighian corpuscles undergoing the obliterative change. Other important changes are to be noticed on the small and medium sized arterioles, their wall being thickened owing to the germination of the nuclei of the muscular tissue; in a considerable number of arterioles the intima is found to be swollen and changed into the hyaline glassy substance, which in some places is so voluminous that the lumen of the vessel is nearly or entirely obliterated. In a later stage the swollen intima appears to change into an indistinctly fibrous substance quite analogous to that into which the glomeruli degenerate. It is interesting to observe that many arterioles next the basis of pyramids show the last-named obliterative changes.

Slight infiltration with lymph-cells may be noticed in the tissue around the large vascular trunks. In one instance I have seen also in the cortex infiltration with lymph-cells of the tissue around a Malpighian corpuscle and between the nearest urinary tubes; the epithelium as well as the lumen of some of these were crowded with them.

There are a few hyaline cylinders in tubes of cortex as well as pyramids, and also in a few instances there were seen in the cortex those deeply stained irregular lime masses.

The epithelium of convoluted tubes shows in a few instances granular disintegration.

The epithelium of ascending branches of Henle's loops and also of some collecting tubes in the pyramids is detached from the membrana propria, and in some places it is breaking up into small elements.

Large blood vessels filled with blood. The vasa recta of the pyramids are distended.

Case 13.—This case shows very little change as compared with the preceding one. It is chiefly: (*a.*) Slight germination of nuclei of muscular coat of arterioles and consequently thickening of the latter. A few peripheral Malpighian corpuscles showing obliterative changes. (*b.*) Infiltration with lymph-cells of the tissue around the large vascular trunks. (*c.*) A small amount of granular matter and blood is contained in some of the Malpighian corpuscles, and the same is seen in convoluted tubes near the pyramids. Blood is contained in some of the large lymphatics of the tissue of calices. In one place there was effusion of blood, in which pigment has already made its appearance, so that it is probably of some duration. The large blood vessels are full of blood.

The urinary tubes in the same condition as in the preceding case, with the addition that some of the large ducts of the papillary part are collapsed or their epithelium quite gone.

Case 14.—The following changes are to be noticed in this case: (*a.*) Thickening of muscular coat of small arteries, swelling up of parts of intima in many arterioles. (*b.*) Thickening of capsule of many peripheral Malpighian corpuscles, in some the glomerulus shows obliterative changes. There are glomeruli in which an increase of nuclei may be noticed, and in several such instances have I found peculiar deeply-stained huge masses, apparently *in* capillary vessels, which masses present the appearances of a well-defined granular lobed nucleus in the act of dividing into two portions connected by a longer or shorter neck, each portion presenting a number of constrictions. (*c.*) Most of the peripheral Malpighian corpuscles which do not show obliterative changes of glomeruli contain granular matter and chiefly masses of blood corpuscles (decolourised). The same material is contained in convoluted tubes, especially in those near the capsule of kidneys.

I must call special attention to this fact (mentioned also in several previous cases), because in the notes furnished to me from the hospital mention was made that the urine in this case had ceased to contain albumen three days before death. In cases 5 and 12 I find in the notes that the urine contained no albumen. It would appear that although Malpighian corpuscles and convoluted tubes contain granular matter—most probably coagulated albuminous matter—and blood, still the urine passed from the kidney did not contain albumen perceptible by the ordinary test. In all these cases the tubes of the pyramids did not show any traces of that albuminous or bloody exudation.

The epithelium of urinary tubes in general shows little change. A few ascending tubes of Henle show detached and disintegrating epithelium. A few tubes of pyramids contain hyaline cylinders. Some of the large collecting tubes of papillary portion appear collapsed, their epithelium shrunk and opaque; in others the epithelium is detached or altogether gone, or it is broken for some distance and the tube filled with granular matter in which a number of different sized very pale and transparent circular bodies may be recognised, probably the well-known drop-like masses which are seen to come out from epithelial structures under very various conditions.

The membrana propria of some large collecting tubes, in which the epithelium has become detached, is opaque and granular, and shows very distinctly membranous processes projecting into the epithelium.

Large blood vessels are filled with blood; the same also in all the blood vessels of pyramids.

I found the deeply-stained globular (lime) masses in the cortex also of this case.

Case 15.—The changes in the kidney of this case are very slight; the following may be observed:—The vessels of the periphery of cortex are very much distended and filled with blood. In some instances the urinary tubes near the capsule appear very much compressed by the distended vessels around. There are arterioles, not in numerous instances though, which show the increase in number of the muscular nuclei, others the homogeneous swelling of intima, and even total obliteration. Likewise there are Malpighian corpuscles, chiefly embryonic ones near the capsule of kidney, the glomeruli of which are in different degrees of degeneration, as mentioned repeatedly before. In the adventitia of some interlobular arteries are contained a few lymph-cells; this is more distinct in connexion with the large vascular trunks,

whence the infiltration with lymph cells extends also on the vasa recta of the basis of the pyramids. The larger veins contain numerous colourless blood corpuscles. Some Malpighian corpuscles and the first part of convoluted tubes contains granular matter; in the latter the epithelium appears opaque and slightly swollen and breaking up into small granular fragments. In a few ascending tubes of Henle (of the cortex) the epithelium is detached from the membrana propria and is breaking up into small elements.

In many collecting tubes of the papillary part the epithelium is also detached from the membrana propria, and is either shrunk into an opaque nuclear mass or altogether gone. The adventitia of the large vascular trunks, especially arteries, contains blood, or appears distinctly stained with blood pigment.

Case 16.—This is the brother of the previous case, whom he survived by one day. It is the first marked case of interstitial nephritis. The kidney exhibits the same features, with the addition that the infiltration with lymph cells in the adventitia of the roots of the interlobular vessels, especially veins, is considerable, *i.e.*, has more advanced than in case 15. Fig. XVI. represents a slight degree of infiltration with lymph cells; as is shown in the drawing they extend already between urinary tubes the epithelium of which is more or less crowded with, and disintegrated by, them; but they are present also along the vasa recta of the basis of the pyramids. It is to be observed, especially in connexion with the latter fact, that thickening is to be noticed in the coats of arterioles, near the infiltration.

Infiltration with lymph-cells may be observed also in parts higher up the cortex, where Malpighian corpuscles, more or less changed, appear to be the centre of the infiltration, from which the lymph-corpuscles extend around and between the urinary tubes of the vicinity. In all cases, however, the medullary rays are free from infiltration. With regard to the lymph-corpuscles of the infiltration, all different kinds may be observed with reference to size of the cell and size and number of nuclei. There are ordinary small colourless corpuscles with two or three small nuclei, then corpuscles with one round deeply-stained nucleus, then there are larger cells with one or two large transparent nuclei.

The epithelium of the first portion of the convoluted tubes is opaque and slightly swollen, in some places it appears to be breaking up into granular particles; some of the large collecting tubes of papillary part contain an opaque, shrunk, and detached epithelium. There are a few hyaline cylinders in tubes of medulla.

The adventitia of some large arterial trunks contains blood.

Case 17.—In the microscopical examination of this case numbers of small foci of interstitial nephritis are found in different parts of the cortex. The intertubular cell-infiltration is seen to be more or less distributed in such a manner that either Malpighian corpuscles, or occasionally also arterioles, or both, appear to be the centre around which the lymph cells are chiefly crowded, and whence they spread between the urinary tubes of the surrounding parts; that is to say, the interstitial nephritis is chiefly limited to the part contained between the medullary rays. The urinary tubes of the infiltrated parts show the changes usually observed in interstitial nephritis, viz., (*a.*) crowding of epithelium and lumen of tubes with lymph-cells; the denser the infiltration the more distinct is this, and the further advanced also are the disintegrative changes of the epithelium; (*b.*) hyaline cylinders in tubes; (*c.*) cylinders composed of exudation cells and of disintegrated

epithelial cells more or less swollen and hyaline ; in the latter case the tube is much distended and the cylinder is composed of distinct hyaline blocks still showing traces of nuclei.

With reference to the lymph-corpuscles of the infiltrated parts, there is nothing to be added to what has been said in the preceding case.

Where the lymph-cells of the infiltrated parts have become removed in the course of preparing the section, it is seen that they are embedded in a meshwork of opaque or granular membranous structures, which network is the more distinct the less there is left of the epithelium of the urinary tubes, so that it is probable that that membranous matrix includes, besides pre-existing intertubular connective tissue, the membranes of the original urinary tubes. This is borne out by carefully examining those places where the exudation-cells gradually replace the epithelium in the urinary tubes.

The Malpighian corpuscles which are found in the infiltrated parts, *i.e.*, in the foci of interstitial nephritis, are in different stages of fibrous degeneration, as described in previous cases (*see* also Fig. XIII., which is taken from a specimen of this case).

So it is also with the arteries of and near those foci ; they show thickening of muscular wall, in some instances swelling of intima or even total degeneration of their walls. The greatest number of degenerated Malpighian corpuscles and arterioles may be found in that part of cortex which is nearest to the pyramids, *i.e.*, in the vicinity of the large vascular trunks ; and in this part are also the most numerous foci of interstitial nephritis.

From this and from the facts mentioned in previous cases we shall draw the inference that the degenerative changes of Malpighian corpuscles and arteries is *not subsequent* to the interstitial nephritis. To this point we intend to return more fully when summarizing the results of our examination of the kidney of the different cases.

The epithelium of some convoluted tubes is swollen, in others it shows granular disintegration. In cortical ascending tubes of Henle the epithelium is detached and breaking up into isolated nuclear elements. The epithelium of collecting tubes and ascending branches of Henle's loops of pyramids is more or less detached from the membrana propria ; in some large ducts of papillary part the epithelium is altogether gone.

The blood vessels of pyramids distended.

There is a considerable amount of yellowish-brown pigment granules contained in the epithelium of first portion of descending branches of Henle's loops.

In one instance a distended urinary tube of cortex contained a huge homogeneous opaque block, including brownish pigment granules.

In a few instances there are the deeply-stained amorphous masses (lime) in distended urinary tubes of cortex.

It is remarkable that the urine did not contain albumen.

Case 18.—The interstitial nephritis, as observed under the microscope, is very considerable in this case ; it is not noticed by the unaided eye except on stained sections, in which the infiltrated portions, *i.e.*, the interstitial inflammation, may be perceived as thin streaks or small patches of deeply-stained tissue in the different parts of the cortex. The greatest amount of infiltration is here also chiefly in parts next the roots of the interlobular arteries, but there are also other parts of the cortex, including the most peripheral portion, in which interstitial change has set in. Next the capsule of the kidney the intertubular tissue is filled with lymph-cells over considerable areas.

As may be expected there are many Malpighian corpuscles in different stages of degeneration ; those that have undergone complete

obliteration are found chiefly near the roots of the interlobular arteries. In the very periphery of the cortex the greater number of glomeruli appear to be impermeable, their nuclei being much increased and the walls of the capillary vessels indistinct, owing to the presence of opaque granular swollen cell-masses.

In connexion with the foci of interstitial nephritis there are certain facts to be mentioned which I have little doubt are likely to throw some light on the nature of the interstitial nephritis. These facts consist in nothing less than embolisms of arteries. In Figs. XIV. and XV. I have selected two of the most characteristic examples; I need hardly say that I have copied these drawings from the preparations with the greatest possible accuracy.

As is shown in one of them, there is a middle sized interlobular artery, which at one place, just where a lateral branch is coming off (cut away obliquely in the preparation), is distended and blocked up by an embolus of considerable size. In the other figure an embolus is shown in an afferent arteriole of a Malpighian corpuscle, just at the point of penetrating Bowman's capsule. Similar "riding" emboli in afferent arterioles and at the same point are present in connexion with many Malpighian corpuscles near the infiltrated peripheral parts of cortex.

We will first describe the nature of the embolus; it consists of different blocks of an apparently amorphous material, including a few cells and nuclei more or less changed. Under a very high power these blocks appear to be granular; they stain slightly with hæmatoxylin and are to all appearance of a fibrinous nature; this is in a great measure supported by the fact that they include cellular structures. In Fig. XV. the lower portion of the artery, *i.e.*, that nearest to the pyramids, contains blood; the upper is more or less empty; at some distance from the embolus it contains numerous lymph-corpuscles. The tissue all round is very intensely infiltrated, and this is more or less also the case in Fig. XIV., *i.e.*, in connexion with the emboli of the afferent arterioles.

The nature of the infiltration or interstitial nephritis is, I think, in no way incompatible with the assumption that it is caused by the embolism of interlobular arteries and their branches, for it quite corresponds to Cohnheim's scheme of inflammation subsequent to embolism of terminal arteries (the arteries of the cortex being terminal arteries par excellence.)

But why should not the embolism of arteries be also the cause of the degenerative process of afferent arterioles and Malpighian corpuscles, as described in this and previous cases? That those obliterative changes are to be observed oftener on the arterioles and Malpighian corpuscles nearest the root of the interlobular arteries, *i.e.*, nearest the large vascular trunks and on the "embryonic" Malpighian corpuscles of the periphery of cortex, seems to me to be much in favour of that assumption; for is it not likely that those minute arterioles which are nearest their large trunks should sooner fall victims to the embolic process than others which are further away? But perhaps there are other special circumstances, hitherto unknown, which determine the greater prevalence of obliterative changes in the last-named locality. The obliteration of embryonic Malpighian corpuscles, however, seems to me to be not incompatible with the theory of embolism, the afferent arteriole of an embryonic Malpighian corpuscle being evidently a vessel out of which there is no exit, or only a very imperfect one, considering that the capillaries of the corresponding glomerulus are only imperfectly developed, or, as in some cases, only very rudimentary.

Now, supposing there are masses circulating in the blood which may

still pass through arterioles and capillaries of well-developed Malpighian corpuscles, is it not possible that they will be arrested in the embryonic glomeruli? And why should there not be masses circulating in the blood which may give rise to the formation of emboli? Are not extensive inflammatory processes going on in the skin, in the throat, and in lymphatic glands, the microscopical characters of which we shall have occasion to discuss hereafter, and in consequence of which changes masses of formed material are carried away from the seat of these inflammations and brought into the circulating blood, which on account of its own changes may be only too favourable to the formation of emboli or thrombi? Thus we shall see afterwards that in lymphatic glands and in some parts of the throat there are blood vessels as well as lymphatics almost completely blocked up by fibrin, or filled with colourless and other cells. But as we shall mention hereafter there are other considerations to be kept in view before accepting this dependence of the obliterative changes on embolism.

In connexion with the interstitial inflammation of the cortex we have to mention similar changes of the urinary tubes as in the preceding case, viz., flooding of the tubes with exudation-cells, and subsequent disappearance of their epithelium, blocking of tubes with fibrinous and cellular masses or with cylinders composed of more or less swollen cells. A few hyaline cylinders, and also amorphous (lime) masses deeply stained in hæmatoxylin. The epithelium of many convoluted tubes shows cloudy swelling, granular and fatty degeneration.

Many descending branches of Henle's loops of papillary part are filled and blocked by deeply-stained (lime) masses or by coarsely or finely granular cylinders.

The epithelium of large collecting tubes of the papillary portion of pyramids appears more or less detached from the membrana propria; in a few instances the epithelium has collapsed and shrunk, into an opaque, relatively small, excentric mass attached to one part of the membrana propria.

The epithelium lining the ascending branches of Henle's loops is also more or less detached from the membrana propria.

There is a considerable amount of pigment in descending branches of Henle's loops of the basis of pyramids.

The muscular nuclei not only of small arterioles but also of the larger trunks are germinating; especially in the latter the muscular coat appears distinctly thickened. In the former the increase of nuclei is well seen at the point of entrance into the Malpighian corpuscle, no matter whether there is or is not an embolus present.

It is remarkable that the urine contained no albumen.

Case 19.—In this case the interstitial inflammation is much more extensive. The tissue around the large vascular trunks is at some places very densely infiltrated, and this infiltration extends also into the basis of pyramids for some distance and into the cortex; in the latter it comprises in some places indiscriminately the medullary rays as well as the tissue between them. Besides places where the cortex is one diffused mass of infiltrated tissue, there are others where only the interlobular artery is surrounded by tissue that has great resemblance to adenoid or lymphoid tissue. The muscular wall of the artery is thickened in a conspicuous manner. The infiltration may be traced from the basis of pyramids throughout the different parts of the cortex. Near the capsule the cortex appears at some places for a considerable distance transformed into a densely infiltrated tissue, in which are discernible more or less degenerated Malpighian corpuscles and

outlines and remains of urinary tubes. The same is the case, to a greater or lesser degree, in those parts in which the infiltration with lymph-cells has reached a high degree.

The greater number of exudation cells contain two or three small nuclei like colourless blood corpuscles.

There are few Malpighian corpuscles which do not present a great abundance of nuclei and are marked by a more or less great opacity of their glomerulus. The cavity of Malpighian corpuscles and of many convoluted tubes contains granular matter and what appears to be remains of decolourised blood corpuscles. As may be expected there are urinary tubes in the pyramids containing numerous exudation cells. The urine examined after death contained albumen.

Finally the thickening of the muscular wall of arteries has to be mentioned.

Case 20.—The interstitial nephritis is still more advanced in this case, but it is limited almost entirely to the cortex, there being only few places where the infiltration with lymph-cells of the tissue around the large vascular trunks extends also into the pyramids. In stained preparations the infiltrated parts are very easily recognised with the unaided eye. The infiltration is either diffuse, *i.e.*, the tissue of the cortex, irrespective of the different sections, becoming gradually more or less densely crowded with lymph-cells, or these latter form cords, a sort of sheath, around interlobular arteries. In the latter case the infiltration bears the greatest resemblance to adenoid tissue, the muscular wall of arteries being at the same time thickened.

All that has been said in the preceding case with reference to the urinary tubes becoming flooded with lymph-cells, and in consequence of this the disappearance of their epithelial cells as such—when the epithelial cells become disunited it is very difficult to recognise them—holds good also in this case. Where the interstitial new growth has reached a certain high degree, and where in the course of preparing the specimen the cellular elements representing the infiltration have become removed, it is seen that they are embedded in a more or less dense network of membranous structures to which is attached here and there a slight amount of granular matter, perhaps remains of disintegrated epithelial cells.

The large venous vessels and the vessels next the capsule are distended and filled with blood.

In parts with considerable interstitial change urinary tubes are to be met with, chiefly Henle's tubes, filled with hyaline cylinders and also with hyaline blocks, the latter in some cases still recognisable as composed of swollen degenerated cells.

A very striking effect is produced by staining these preparations with acetate of rosaniline, for the interstitial new growth, or rather the nuclei of the cells constituting it, and the nuclei of the epithelial cells of urinary tubes, appear of a pink-violet colour; both the normal as well as the degenerated Malpighian corpuscles, the blood vessels, connective tissue, the hyaline cylinders in the urinary tubes, and the membranes of urinary tubes, are of a pale blue colour.

There is granular and fatty degeneration of the epithelium of some convoluted tubes.

The urine did not contain albumen.

The next cases deserve as much attention as those we minutely described in the preceding pages, but I should be afraid to weary the reader if I were to repeat all the appearances mentioned in the last two or three cases over again, for, as may have been already expected by

this time, we should probably find interstitial nephritis of a more advanced degree in cases where death has set in at a later period than in the preceding two or three ; and this is actually what we find in—

Case 21.—The infiltration is very intensive in the tissue of calices, and extends hence into the tissue surrounding the large vascular trunks, and further into the cortex and the basis of the pyramids. There are also here extensive parts of cortex which show considerable infiltration, amounting to more or less total disappearance of urinary tubes, but we have to notice likewise the presence of cords of infiltrated tissue closely resembling adenoid tissue forming a sheath round interlobular arteries, the muscular coat of which is at the same time thickened, the nuclei of the muscle-fibres being actively germinating. From the sheath of the artery the infiltration extends between the urinary tubes for a variable extent.

All that concerns the changes of epithelium of urinary tubes and their contents, in infiltrated as well as in uninfiltrated parts, as described in the preceding cases, is likewise to be observed in this case, with the addition that the hyaline cylinders are relatively numerous in the tubes of pyramids, where there are also tubes filled with cylinders composed of swollen degenerated cells, and further cylinders composed of more or less coarsely granular matter, or of that globous material which we previously declared to be lime matter. With reference to the last-named structure I have to mention one interesting fact, which is this : there are branches of Henle's loops in the papillary part, the epithelial cells of which are changed in some parts into granular cells of considerable dimensions ; now within these cells, and extending also into the lumen of the tube are droplike or oval hyaline bodies fused together so as to form cylinders, or the epithelium contains globular transparent structures very sharply outlined and in their outline deeply stained. These structures are forming chains of a more or less complicated nature ; they are in some instances plugging the whole tube. In one instance I have distinctly seen a portion of such a chain perforating the membrane of the tube so that a small part of the chain was lying outside, just as if a mycelium had grown through the tube. *See* Fig. XXXIX. In some tubes this material looks as if composed of spherical or oblong sharply outlined cells—about a little smaller than coloured blood corpuscles—possessed of a very thick cell wall stained deeply with hæmatoxylin, and as if they formed longer or shorter more or less complicated (branched or lobed) chains. These quasi-cells vary, however, very much in size, and are, no doubt, of an inorganic nature, probably lime salts. At some places they do not desemble nuclei of epithelial cells in the act of germination. It is not the individual particle of the material in question upon whose nature we are to make a definite diagnosis, but it is here as in many other circumstances, the relation of these particles towards each other and the surrounding elements, their grouping, their aspect, and the different conditions in which they are met with, upon which a diagnosis is justified. In this case we have only to look at different tubes of the papillary part to see that between the cylinders composed of the above-mentioned chains of globous bodies, and those deeply-stained more or less amorphous irregular lumps by which some tubes are completely blocked up, there exist all transitional forms. And this is one of the chief reasons why I regard the substance in question of the nature of urinary salts, which have been precipitated either on their way into the epithelium, or in this latter.

From a careful study of the relation of these masses to the urinary tubes I have come to the conclusion that they are contained originally

in the epithelial lining, even where they form large masses by which the tube becomes blocked up and distended. Where this has reached a high degree it is understood by itself that the epithelium has given way and disappeared altogether.

The coarsely granular masses are chiefly contained in large collecting tubes, whereas the above-mentioned lime matter is found chiefly in Henle's tubes.

The epithelium of the large ducts is transparent, the interepithelial nucleated septa extending from the membrana propria between the epithelial cells are very distinct. Some epithelial cells are very much swollen and transformed into goblet cells.

In a few ducts the epithelial lining is detached from the membrana propria, opaque, folded, and shrunk. A similar condition is observed in the epithelium of some collecting tubes of cortex.

Case 22. — Here we have interstitial nephritis of the same character as in the preceding cases. There is to be mentioned the fact that the blood vessels, capillaries, and veins of the periphery of the cortex are in some parts distended and filled with blood; these parts not very extensive and are marked by a diffuse infiltration of the intertubular tissue with more or less numerous lymph-corpuscles, the epithelium of the urinary tubes of these parts being detached from the membrana propria. The same condition with regard to tubes and blood vessels is present in some parts of the basis of pyramids.

The changes of the epithelium of convoluted tubes are very marked, consisting in cloudy swelling in some, granular and fatty degeneration in others. Numerous tubes (Henle's ascending branches) in cortex contain hyaline cylinders, others contain cylinders composed of cells more or less swollen up.

In some infiltrated parts where the epithelium of the urinary tubes is breaking up in consequence of being overcrowded by lymph-corpuscles, some of the epithelial cells possess two or even three nuclei.

With reference to the urinary tubes of pyramids there is one fact especially to be mentioned, viz., the membrana propria of large collecting tubes, as well as the intertubular and intervascular connective tissue of some parts of the papillary portion of pyramids, is swollen up and converted into a homogeneous substance. Some of the tubes of Henle contain masses composed of smaller or larger droplets, similar to fat-droplets, but they are different from true fat-droplets inasmuch as they are not dissolved by alcohol, oil of cloves, &c. There are also tufts of what appears to be fatty crystals contained in some Henle's loops.

The epithelium of ascending branches of Henle's loops and of many collecting tubes is detached from the membrana propria, and is in some instances breaking up into small fragments.

Case 23.—This forms the last case; as the reader remembers from the first chapter, this patient had recovered from the acute attack of scarlatina, when he was taken ill with pneumonia, on the eighth day of which he died. The changes that I found in the kidney are as follows :—

Many glomeruli show an abundance of nuclei ; in some of them the capillary vessels are very indistinct, being replaced by an opaque or granular substance in which the nuclei appear to be obliterated.

In some arteries the wall is much thickened, owing to the increase of muscular tissue, but also the nuclei of the endothelium appear to be increased in numbers. In a few instances I have seen arterioles in a state

of obliteration. There are present in some parts of cortex a few lymph-corpuscles between urinary tubes and also around arterioles. The same condition is met with in the basis of pyramids. The chief changes, however, are to be observed in the urinary tubes; in some of the convoluted tubes is contained granular matter and blood; the epithelium is in a state of disintegration. In some ascending tubes of Henle of cortex and likewise in some collecting tubes of pyramids the epithelium is detached from the membrana propria and breaking up into granular fragments. The epithelium of large collecting tubes of the papilla is entirely gone.

Many ascending tubes of Henle and also collecting tubes of cortex contain hyaline cylinders and cylinders including more or less changed blood corpuscles. The same is also the case with many tubes of pyramids.

There are numerous tubes in the cortex (a few also in papillary part), chiefly Henle's tubes and collecting tubes which contain the deeply-stained (lime) matter.

B.—*General Remarks on the Anatomical Changes of the Kidney.*

If we now summarise the results of our examination, we may, I think, without reference to any theory, divide them into (1) those belonging to the early, and (2) those belonging to the later changes.

1. Amongst the former we found (*a*) the peculiar degenerative changes of arteries and Malpighian corpuscles, (*b*) the germination of nuclei in the wall of arteries and in the glomerulus, and (*c*) slight alterations of the epithelium of certain tubes in the cortex and pyramids.

(*a.*) The intima of arterioles of cortex undergoes a peculiar change, swelling up for a greater or smaller part of the circumference, and for a various extent into a hyaline substance which is of a bright glassy aspect, and as the process advances splits more or less distinctly into fibrillæ. This change occurs generally on the afferent arteriole next the Malpighian corpuscle; it may lead in some cases to a perfect occlusion and obliteration of the vessel, the change having spread to all layers of the wall. A similar process is to be observed also on the glomerulus of Malpighian corpuscles; in the slighter degrees the wall of capillary vessels appears from place to place thickened, having swollen up into a hyaline substance, it is granular and opaque, and the nuclei are germinating very much; these nucleated masses become more or less fused into a hyaline material, which finally undergoes a more or less distinct fibrous degeneration. The capsule of the Malpighian corpuscle during this time is much thickened, at first homogeneous, containing many oblong nuclei, and then also becoming fibrous.

(*b.*) The nuclei of the endothelium and especially those of the muscular coat of arterioles are in a state of active germination; this is chiefly observed in afferent arterioles, but also in interlobular arteries and even in the large arterial trunks; the wall of some of the afferent arterioles and interlobular arteries is conspicuously thickened. Where the hyaline degeneration of the wall of an arteriole has advanced to a certain degree, very little or nothing is left of the muscular coat.

(*c.*) We observed swelling up of epithelium of some convoluted tubes and germination of the nuclei of the epithelial cells, especially conspicuous on a portion of a cortical ascending tube of Henle lying next to an afferent arteriole. Granular matter and blood in Malpighian corpuscles and some portions of convoluted tubes was almost generally

observed; also slight cloudy swelling and granular disintegration in some tubes of cortex. The changes of the tubes of the pyramids were only very slight. This is very much in accordance with the observations of other pathologists, although I think my observations refer to earlier cases. With the exception of the conspicuous increase of nuclei of a certain part of a cortical ascending tube of Henle, the other changes of urinary tubes are devoid of a special significance, being no doubt dependant upon the congestive condition of the kidney. The loose connexion of the epithelium with the membrana propria in ascending branches of Henle's loops of pyramids and of the large collecting tubes of this same region, especially of the papilla, is, no doubt, a result of the same condition. But whether the removal of the epithelial lining of some of the last-named tubes, as observed in some cases, is taking place intra vitam or post mortem is not easily ascertained. Rindfleisch on the occasion of desquamative catarrh of the kidney (Handbuch der Pathologischen Histologie, p. 448), says that on applying lateral pressure on the papilla of any not quite fresh kidney, one invariably expels a certain amount of epithelium from the urinary tubes, and we are therefore, from the absence of the epithelial lining in sections, not justified in concluding that this absence indicates that the epithelium had been removed intra vitam. Looking now at our cases, and considering that the kidneys were obtained and put into the hardening fluid in many instances within a short time after death, that in some of the cases the urine did not contain albumen, and that the epithelium of the collecting tubes did not show any conspicuous alteration, it seems probable that the absence of the epithelium in the collecting tubes is not a purely accidental symptom. The fact that in some of the collecting tubes the epithelium is occasionally seen to break up into small granular elements is no doubt greatly in favour of the non-accidental character of the symptom in question. On the other hand, it must be admitted that "the abundant production of young cells by the connective-tissue "around the urinary tubes inducing a secretion of numerous young "cell-forms" (Rindfleisch, l.c., p. 449), as chief part in desquamative catarrh, is altogether absent in our early cases.

With regard to the changes of arterioles and Malpighian corpuscles above mentioned, there is very little known hitherto. Klebs (Handbuch der Pathologischen Anatomie, III. Lief. p. 645) describes under the name of glomerulo-nephritis a condition of the kidney which he found in scarlatina during the period of desquamation, when the patients appeared to have been perfectly convalescent. There was œdema of the face, &c., then scarce urine, or complete retention, followed on after by uræmic poisoning. "In the post-mortem examination the kidneys "are found slightly or not at all enlarged, firm . . . . , the parenchyma "very hyperæmic. Only the glomeruli appear on close inspection pale, "like small white dots. The urinary tubes are often not changed at "all, occasionally the convoluted tubes are slightly cloudy. The micro-"scopic examination shows that there are neither interstitial changes "nor germination of epithelium, the so-called renal catarrh, generally "supposed to be present under those conditions on account of the "absence of other perceptible derangements, and there seems therefore, "leaving out the glomeruli, the congestion of the kidney alone to "remain to account for the symptoms during life. That this, however, "is insufficient no one can doubt, knowing that in equally intensive "active as well as passive hyperæmia, *e.g.*, in CO poisoning and in "passively congested kidney, complete anuria and acute uremia never "happens." On microscopic examination of the glomeruli it is seen that "the whole space of the capsule is filled with small somewhat angular

nuclei, embedded in a finely granular mass." "The vessels of the glomerulus are almost completely covered by nuclear masses." Klebs has convinced himself that we have to do here with a germination of the cells in the interstitial connective tissue of the glomerulus (first pointed out by Axel Key), in consequence of which the vessels of the latter become compressed.

As the reader probably remembers, we have observed in all our early cases the great abundance of nuclei of the glomerulus, but a condition like that described and figured by Klebs (Fig. 72, p. 646) I have met with only in very few glomeruli. I am not less certain that in our cases the nuclei of the epithelial elements on the surface of the capillary blood vessels of the glomeruli are germinating, being either in state of division or already divided. Of these epithelial elements Klebs only mentions that in some cases they are fattily degenerated, a condition which in these early stages I have never met with. The cases of Klebs (I cannot gather from his description how many cases he refers to) were, I have little doubt, different from those I examined, for a general condition of the glomeruli as described by this observer, and such an excessive germination of nuclei that the blood vessels are completely compressed, was not seen in one of the 23 cases I have examined. In two cases, 9 and 10, the kidney had been injected artificially very soon after death, and it was found that with one or two exceptions all glomeruli are permeable, a result at which I was not a little surprised, for in uninjected preparations many glomeruli give one the impression of being impermeable, a condition which Rindfleisch well appreciated under other circumstances, and therefore rightly advises to examine the injected kidney. I must therefore question whether the anuria and uræmic poisoning in scarlatina, when the kidney does not show any conspicuous catarrhal or other changes, is due to a *compression* (Klebs) of the vessels of the glomeruli by the nuclear germination. I am inclined rather to insist on the changed state of the arterioles. In all our cases we have seen an overgrowth of the muscular tissue in the arterioles; and if this may be taken to express that under the influence of some stimulus (perhaps some blood irritant) which the disease supplies, the arterial muscular tissue has been exceptionally exercised; query, whether this exceptional exercise of contractility, affecting the calibre of arterioles, may during life shut the glomeruli out of the circulation, and may thus, so far as it operates, suppress the secretion of urine.

The degenerative changes of arterioles and Malpighian corpuscles which we described in our early cases have not been noticed by any of my predecessors. A hyaline degeneration of vessels, it is true, has been described before now, but not in the kidney of early cases of scarlatina. Thus Gull and Sutton (Medico-chirurgical Transactions, volume 55, 1872, p. 273) observed a peculiar alteration of arterioles in chronic Bright's disease, which (alteration) has a certain resemblance to that noticed in our cases. These authors found (l.c., p. 283):

"(1.) That the arterioles, throughout the body in that condition usually called chronic Bright's disease with contracted kidney are more or less altered.

"(2.) That this alteration is due to a "hyalin-fibroid formation in the walls of the minute arteries, and a hyalin-granular change in the corresponding capillaries.

"(3.) That this change occurs chiefly outside the muscular layer, but also in the tunica intima of some arteries.

"(4.) That this change in different organs varies in different cases.

"(5.) That the muscular layer of the affected vessels is often atrophied in a variable degree."

The chief difference between us is, that in my cases the hyaline change is limited entirely to the intima of arterioles. In both cases the hyaline change extends also on capillaries (*see* our observations about the capillaries of glomerulus).

Fr. Neelsen (Archiv. der Heilkunde, 1876, II. and III. Heft, p. 119) noticed in various cerebral diseases, in many acute infectious diseases (variola, typhus, morbilli, one case of scarlatina), and in various other diseases (syphilis, phthisis, pneumonia, dysenteria, rheumatism, &c.), the wall of capillaries of the pia mater considerably thickened, highly refractive, and of a lardaceous aspect. Generally only small portions of the capillaries are thus affected, most frequently at the point of branching into two or more branchlets. The nuclei of the endothelial cells of those parts are never normal, always shrunk. In a few cases Neelsen saw also in some isolated arterial branchlets passing into capillaries a thickening of the wall extending for a large distance, and consisting in a fusion of the intima, media, and adventitia into a colloid mass, in which at some places were included amyloid bodies. The chemical examination proved that the substance in question has similar properties as elastic tissue. Several observers (Lubimoff, Rudolf Arndt, Schüle, Adler, and Eppinger) had previously described a waxy, colloid, or glassy degeneration and thickening of capillaries and smaller vessels of the pia mater, and have associated this morbid condition of the vessels with certain diseases of the cerebrum; by the observations of Neelsen this conclusion appears unjustified. With regard to the development of that colloid or hyalin change of capillaries, Neelsen arrived at the conclusion that "the degeneration starts from the endo-"thelium. The nuclei commence to shrink, the endothelial cells "become fused into a colloid mass, which extends excentrically into the "perivascular lymph space, and finally fills this completely . . . . . A "narrowing of the lumen seems to result not at all, or only in a very "slight degree." There can be no doubt that Neelsen observed a change which belongs to the same category as that noticed by Gull and Sutton. Neelsen's colloid degeneration bears likewise a great resemblance to the hyalin degeneration observed by myself on the arterioles and capillaries of glomeruli with this difference, that in our case the endothelium of the arterioles has nothing whatsoever to do with the degeneration in question; only very late, when all the layers of the arterioles become involved in the degenerative process, there is likewise a change of the endothelium. In the capillaries it is of course different, for their wall is only endothelium. Two points in Neelsen's observations are of very great interest to me: (1) the fact that the hyaline change affects very readily the vessels near their point of branching, and (2) that the hyaline substance in question is of the nature of elastic tissue; for in the kidney of our cases, the afferent arterioles undergo the change in question chiefly near their termination, *i.e.*, near the point of branching into the capillaries of the glomerulus, and the intima being the part of the arteriole which undergoes the hyaline degeneration, it is quite clear that for this reason this substance is of the nature of elastic tissue. I am inclined to think that in the arterioles observed by Gull and Sutton it is also an elastic layer which first undergoes the hyaline change; not the intima but the external elastic layer, *i.e.*, that separating the media from the adventitia. As I mentioned already, in the kidneys of our cases of scarlatina the hyaline change invariably attacks the intima, and only when the degeneration has proceeded far enough, also the other coats become more or less involved in the process.

In my paper "On the Minute Anatomy of Typhoid or Enteric Fever,"

(*see* these Reports, 1875,) I have described and figured a change of arteries of the intestine and spleen, which is the exact counterpart of the changes observed in the arteries in scarlatina; in that paper I called the change a deposit of colloid material between intima and media, but looking at the drawings and my old specimens again, I find that it is precisely the same hyaline degeneration of the intima of the vessel as in scarlatina.

Let us now pause for a moment and inquire into the cause and effect of the changes of minute arteries referred to in the preceding. On superficial consideration it seems reasonable to suppose that the germination of muscular nuclei of arterioles is a consequence of the degenerative change of the ends of arterioles and of capillaries of glomeruli; that is to say, inasmuch as by the swelling of the intima at the termination of afferent arterioles, and a corresponding swelling of the wall of some of the capillaries of the glomerulus, the resistance, already great under normal condition, becomes excessive, the muscular coat of the afferent arteriole will become hypertrophied. This, as I said, seems at first sight an admissible explanation, but looking carefully at the facts I do not regard it as the correct one. The chief reason for saying so is this: the number of arterioles and glomeruli in which the above degenerative changes may be observed is very small as compared with the number of arterioles and arteries, whose muscle nuclei are in a state of germination. In several of the above cases we have seen the great increase of muscle-nuclei and hypertrophy of the muscular coat in even large arterial branches of kidneys where only very few arterioles and Malpighian corpuscles presented the changes in question, and therefore I cannot but think that the germination of muscle nuclei in arteries is in no way dependent upon the hyaline degeneration of vessels. Besides the additional amount of resistance caused by this hyaline swelling could not in early stages be so great as to cause so conspicuous a hypertrophy of the muscular coat we actually meet with in a great number of arteries.

I am inclined to think that both the hyaline degeneration and the germination of muscle nuclei we meet in earlier stages are two concomitant symptoms, caused probably by the same agent. Why should not peculiar conditions of the blood—(not exclusively the scarlatinal state, for the hyaline degeneration occurs as we mentioned in many other pathological conditions, acute infectious and other febrile diseases, cerebral diseases, &c.)—affect the walls of the vessels in that peculiar way? and if the blood coagulates when in contact with the non-healthy wall of a vessel, why should not vice versâ a morbid condition of the blood react on the wall of the vessels, considering the intimate relation that exists between the two tissues? I am of course far from denying that if in our cases or others the end of an arteriole becomes narrowed, the wall of the arteriole will cæteris paribus become hypertrophied; but what I think I am justified in saying is that the germination of muscle-nuclei and the hypertrophy of the muscular coat, as observed in earlier stages of scarlatina, are not dependent on the hyaline degeneration of the intima of the ends of arterioles and of capillaries of glomeruli, but that both are probably dependent on the same cause lying in the blood itself. We shall see afterwards that the hypertrophy of the muscular coat is found also in other organs, *e.g.*, tongue, epiglottis, tonsil; of the same condition in the arteries of the skin we have already had occasion to speak, where no such hyaline degeneration of the intima can be ascertained. And finally we shall have to mention, on the occasion of the spleen, that very extensive hyaline degeneration takes place in arteries without any conspicuous hypertrophy of their muscular coat. All these facts are to be considered in discussing the relation of the two processes towards each

other, viz., the change of the muscular coat and the hyaline degeneration. As the reader may have already observed, all these facts do not seem to be quite in conformity with the hypothesis hinted at in a former page of this memoir, viz., that the degenerative changes of the arterioles are due to embolism.

Not less important is the question what effect has the degeneration of arterioles, and especially that of Malpighian corpuscles? I think I am safe in saying, none which is clinically appreciable; there is in some parts a slight increase of the connective tissue around—chiefly increase of nuclei, sometimes also a few round cells; but the number of Malpighian corpuscles undergoing the hyaline and fibrous degeneration is after all not large enough to have any but slight effect. In later stages when interstitial nephritis has become a conspicuous feature the number of Malpighian corpuscles degenerated in the above-manner is not greater in some cases than in the earlier stages. The explanation that the degenerative changes of arterioles and Malpighian corpuscles should not have any other than a slight effect is, I think, not only due to the *relatively* small number of arterioles and Malpighian corpuscles affected in that manner, but probably chiefly to the slow progress of that degeneration, so that sufficient time is allowed for the surrounding vessels to adapt themselves to the new conditions. Before leaving this question of the hypertrophy of the muscular coat of arteries of the kidney I must mention that such a condition has been, so far as I know, first pointed out by Dr. George Johnson in Bright's disease; his view on the causes of that condition of the arteries is too well known to be here gone into.

When describing some of the earlier cases I intentionally laid some stress on the fact that the degenerative change of arterioles and Malpighian corpuscles is not subsequent to interstitial nephritis; and if hereafter we shall mention the condition represented in Fig. XIII., in which two more or less degenerated Malpighian corpuscles are seen to be surrounded by inflammatory products, the reader will have to bear in mind that this condition is very well compatible with the above proposition, for as we shall mention below, the inflammatory condition and degeneration of Malpighian corpuscles *in this and in similar instances* are caused by one and the same agent, *i.e.*, embolism of afferent arterioles.

There is one other point which is of great interest to the pathologist; it refers to the presence of granular matter and remains of blood so often observed in Malpighian corpuscles and convoluted tubes in portions of the kidney in many of the earlier cases. That this granular matter is partly due to exuded and coagulated albuminous matter and partly to the disintegration of epithelial cells, has already been mentioned, and likewise that the urine in some of the cases did not contain any albumen. The explanation of this phenomenon may be either that the quantity of albumen passing out of the kidney into the urine is after all too small to be detected, or that the albuminous matter present in the above-named localities does not leave the kidney at once, but remains stationary or almost so for a longer or shorter time. This latter seems to me to be more probable, since it is a fact well known to physicians that albumen may appear and again disappear in the urine of scarlatina patients in a very irregular manner and without any appreciable cause, as far as the general character of the disease is concerned. Is it not probable that either in consequence of the above-mentioned cramp of arterioles (*see* a former page), and subsequent impeded circulation and secretion in the corresponding parts of the cortex, the exuded matter is not carried away from the convoluted tubes until that cramp of arterioles passes off and the secretion is resumed again?

2. We come now to the later changes, as which we have particularly described (*a*) the appearance of the round cells, lymphoid cells, or whatever they may be called, in the connective tissue of the kidney, *i.e.*, the interstitial nephritis, and (*b*) certain concomitant alterations of the urinary tubules. As we have mentioned above in detail already, (*see* first part of this chapter) the infiltration with round cells is observable at the end of the first week in the connective tissue around the large vascular trunks, (which is a continuation of the deeply-situated connective tissue of the calices) whence it spreads into the basis of the pyramids, and especially into the cortex: The gradual increase in extent and intensity of this infiltration is so decided in our cases (*see* cases 11, 18), that I have no hesitation in concluding that the interstitial nephritis, when it does take place, commences about the end of the first week as a slight infiltration of the tissue around the large vascular trunks, and cæteris paribus gradually increases to such an extent that portions of the cortex, very seldom portions of the basis of the pyramids, are converted into a pale, firm, round-cell tissue, in which the original urinary tubes of cortex become gradually quashed and lost. Some of the urinary tubes contain hyaline or more or less swollen cellular cylinders, others show granular or fatty degeneration. We have pointed out before that the changes in question of the urinary tubes, in parenchymatous nephritis, viz., crowding of urinary tubes with lymphoid cells, granular and fatty degeneration of epithelium of urinary tubes, and cylinders of different kinds in the tubes, become distinct after the interstitial changes have reached a certain high degree, and that they are quite insignificant before this degree of interstitial nephritis is attained. The infiltration of cortex with round cells is first observable at the roots of the interlobular vessels, whence it spreads very rapidly towards the capsule of the kidney, and also laterally among the convoluted tubes around the Malpighian corpuscles. The infiltration is at first limited to the tissue between the medullary rays, *i.e.*, the parts around the interlobular vessels ; later on it encroaches also on the medullary rays and attacks extensive portions of the subcapsular region. In the course of this process considerable parts of the peripheral cortex—occasionally of a more or less distinct cuneiform character with the basis nearest the capsule of the kidney—become converted into whitish, firm, bloodless, cellular masses, in which Malpighian corpuscles and urinary tubes cannot be more than imperfectly recognized. When the infiltration of cortex has reached so high a degree that it can be perceived in a section already with the unaided eye, it will be found that many Malpighian corpuscles in the midst of the foci of infiltration have more or less completely degenerated into fibrous masses, containing the remnants only of nuclei ; this degeneration is not to be confounded with the degeneration observed in the earliest stages, when no interstitial inflammation has made itself felt as yet.

The infiltration of the pyramids was altogether of rare occurrence in our cases, it did not exceed the basis of the pyramids, and was altogether limited to the surroundings of the vasa recta.

That in some cases the infiltration in the cortex, especially around interlobular arteries, presents all the characters of adenoid or lymphatic tissue, *i.e.*, more or less dense reticulum of fibres or membranous structures, in the meshes of which lie embedded chiefly uni-nuclear lymph-cells, has been mentioned in detail in the first part of this chapter, and likewise that in the course of the increase of the round-cell tissue between convoluted tubes the epithelium and the membrana propria of these latter are gradually losing themselves in the new growth.

It is not necessary for me to dwell any more on the characters of the interstitial nephritis in our cases, for they are in every respect

identical with the earlier stages of interstitial nephritis in general, not only as regards the nature of the cell-infiltration, but also that of the urinary tubes (*see* Rindfleisch, l.c., p. 458). From the preceding description and from the drawings accompanying this paper, it is established beyond doubt that we have to do with that condition, viz., interstitial nephritis, and what is of paramount importance, that this change makes its appearance already at the end of the first week, and after this time gradually goes on increasing. In order to remove any misunderstanding I will add that I am speaking only of my own cases, *i.e.*, of cases which died in the course of, and from, scarlatina; my remarks on the interstitial changes do not refer to those that recover, or those that die in the course of scarlatina through another disease.

The most important question with reference to the interstitial nephritis is that of its intimate ætiology. In reviewing the above-mentioned changes with a view to ascertain how far they may be directly concerned in causing the interstitial inflammation we may without much hesitation dismiss: (*a.*) the degenerative changes of arterioles and Malpighian corpuscles as occurring in the earlier stages; they cannot be the inducing cause of the interstitial nephritis, considering that the latter is, in respect of locality, altogether independent of those degenerative changes; (*b.*) the changes of urinary tubes; this point we have already discussed and dismissed before. Remains now the embolic process. The presence of emboli, which we found in case 18 so abundantly, and which we described fully on a former page, was in that case, I think, clearly the cause of the interstitial nephritis. In connexion with this it must be borne in mind that the degenerative changes of the arterioles so often mentioned is probably of no small import for the embolic process, for the simple reason that an arteriole become considerably narrowed by the local hyaline degeneration of its intima and therefore impermeable for formed material of a certain size that happens to be circulating in the vascular system. That abnormal masses of formed material are carried into the blood from the different seats of inflammation (skin, throat, lymphatic glands) in the earlier stages of scarlatina is a point which does not require any proof. Granted the affluxus of abnormal masses of formed material into the circulating blood, it becomes very probable that considering the condition of the blood—being very easily coagulable, as is shown by the masses of fibrin present in blood vessels of the different organs—these masses may become centres of fibrinous deposits, and thus by their increasing size may become a source of extreme danger.

From the identity of the appearances respecting the interstitial nephritis of case 18 with those of the other cases of the same category, it would seem possible that also in the latter the interstitial inflammation may have been caused by emboli; but in fact such were not seen.

In conclusion, we have to mention the very curious fact of the deposit of what we regarded as lime-matter in the epithelium of urinary tubes, first of cortex, then also of pyramids, at a relatively early stage of scarlatina, and at a time when otherwise the kidney shows but little change. Is this deposit or precipitate of lime-matter due to an abnormal amount of it in the blood, or is it not rather due to some sort of abnormal functional condition, of the epithelium? The latter seems to be the more probable explanation.

We have now to see in what manner my assertions of the changes of the kidney coincide with, or differ from those of previous observers. As we have had occasion to state, there were only very slight changes in the urinary tubes; in the earlier stages where no interstitial nephritis was present, they could be detected only on very careful

examination of stained sections of well-prepared material. My cases are therefore different from those of some other writers (the literature of this subject see in Professor Thomas's Article) whose observations refer to cases of well-marked parenchymatous nephritis.

With regard to the interstitial change of the kidney in scarlatina Thomas says, (l.c., p. 230) "Circumscribed inflammatory masses are "found diffused throughout the stroma, or only at certain points of the "same, resembling abscesses and composed of small round cells, the "whole presenting an appearance of interstitial or purulent nephritis." From this not very circumstantial description I am unable to see whether Thomas merely refers to the cases he quotes from E. Wagner and Biermer, or whether he regards this as an usual occurrence, and if so at what stage or stages does it occur? Beyond those sentences there is nothing to indicate that in the majority of cases of nephritis anything else is meant but parenchymatous nephritis.

Biermer (An unusual case of Scarlatina, Virchow's Archiv. Bd. 19, p. 537), in a case of scarlatina in a boy of $5\frac{1}{2}$ years old, which lasted from May 4th until June 8th, 1858, finds the following condition of the kidney: both kidneys are much enlarged, about as large as in the adult; "they have also experienced an extensive and recent new "formation of connective-tissue, in such a manner that the stroma is "very marked with many nuclei, whereas the urinary tubes are filled "with delicate, partly somewhat irregular, slightly granular, otherwise "unaltered, cells. In the cortex, and still more distinct in the basis of "the pyramids, numerous roundish white patches may be perceived of "about the size of hemp-seeds." On microscopic examination it is found that these white patches are due to masses of small stellate cells very closely situated, and thus almost perfectly concealing the other tissues. Similar connective-tissue new growths were present in the liver and spleen; of this, see below.

E. Wagner (Beitrag zur Patholog. Anatomie der Scharlachs, Archiv. der Heilkunde, 1867, p. 262) records a case of scarlatina with "lymphatic new growth" in the kidney. This refers to a lad of 17, who died after 48 hours' illness. "The cortical part of the kidney "contained numerous small circumscribed groups of cells and nuclei, "partly and chiefly in the next neighbourhood of Malpighian cor-"puscles, which latter were of smaller size. All the epithelial ele-"ments of the kidney show a greater or smaller albuminous (cloudy) "swelling, especially those of Henle's loops. Considerable numbers "of urinary tubules contained either pus-corpuscles only, or besides "the latter also epithelial cells showing albuminous (cloudy) swelling." Similar lymphatic new growths were present in the liver and spleen of this and a second case, of which more hereafter.

Dr. T. Coats describes (in British Medical Journal, 26th September 1874) a case of "acute interstitial inflammation of the kidneys in "scarlet fever, fatal on the tenth day." At the post mortem examination both kidneys were much enlarged. They presented to the naked eye very much the appearances of the large white kidney, the cortical substance being very pale and much increased in thickness. "The microscopic characters in this case were quite unequivocal. "The enlargement and paleness of the kidney were due to an infil-"tration of the cortical substance in almost every part by multitudinous "round cells. These were packed in between the tubules, separating "them, but not to any great extent destroying their epithelium. "The cells were about the size of white blood corpuscles." . . . . .

"The epithelium of the renal tubules was very little changed, "perhaps slightly enlarged and granular." . . . . .

Klebs, l.c. p. 465, makes a short remark to the effect that there are "patients who sooner or later after the disease (scarlatina) has "passed away perish from diffuse interstitial nephritis and its sequelæ." From what we have shown it is clear that the case of E. Wagner, as well as that of Biermer and also of Coats, do not form any exceptions from the general rule which we have laid down, viz., that in all cases that die during and from scarlatina, after a certain time, generally after about one week, the kidney is the seat of more or less marked interstitial nephritis. At first the inflammation is so slight and the places of infiltration are so scarce, that it requires careful examination to detect them; they become well marked as the disease proceeds. If the stage is reached in which the foci of interstitial inflammation are numerous and extensive, the kidney shows a perceptible increase in size and a conspicuous increase in thickness of cortex, which at the same time is exceedingly pale. In the earlier stages, *i.e.*, when there are only slight interstitial changes. the kidney is not enlarged, and its cortex is not paler than is usually found at this stage of scarlatina. It is probable that the interstitial nephritis in many early cases (after the first week) has been overlooked by other writers on account of its very slight degree. Only in this way can I account, on the one hand, for the absence of a record of cases with slight degrees of interstitial nephritis, and on the other hand, for the case of E. Wagner, Biermer, and Coats being described as "unusual cases." According to me they are not unusual in manner, they are only unusual in degree. Wagner's case is, besides, unusual also as regards time.

IV.—Examination of the Organs of the Throat.

(A.) *In the above Cases.*

The organs of the throat, *i.e.*, tongue, palate, tonsil, pharynx, larynx, and trachea have been examined of Cases 1, 4, 5, 6, 9, 11, 20, and 22.

We shall describe in the first section of this chapter the results of the examination of tongue, palate, tonsil, and pharynx, and in another section those of the larynx and trachea.

1. *Tongue, Palate, Tonsil, and Pharynx.*

Case 1.—The tongue shows in all parts signs of inflammation. They are enormous increase of the thickness of the epithelium; the nuclei of epithelial cells are very numerous in the deeper strata. The epithelium is much infiltrated with migratory cells, mostly containing two or three small nuclei like colourless blood corpuscles, these latter chiefly accumulating in the superficial layers of the epithelium in smaller or larger cavities; hence very little is left of the original epithelial cells in the superficial strata; only a honeycomb of membranous structures remaining in their place. A division and proliferation of the nucleus of the epithelial cells in the superficial layers may easily be proved (*see* Fig. XX.). In many parts, especially on and near the tops of papillæ fungiformes, the intercellular clear spaces previously mentioned (*see* the examination of skin in the first cases) are very distinct, and so are also the smaller or larger distensions of them, containing, as has been already stated, migratory cells.

At the side of the tongue there are extensive places where the epithelium as well as the subjacent mucous membrane and muscular tissue are converted into a firm, dry, opaque, necrotic mass.

The connective tissue of the papillæ is very much infiltrated with lymph cells, so that the papillæ are very much increased in length as

well as in thickness. The minute blood-vessels are much distended, and their endothelial nuclei increased in numbers. This is especially well shown when the wall of a small vessel is looked at in the horizontal view. Many nuclei show marks of division, or being situated in couples or small groups of three and four. A peculiar aspect is presented by the endothelial nuclei in some of the smaller vessels, viz., showing a longitudinal linear mark (*see* Fig. XXIV.). The nuclei of the muscle fibres of the wall of small as well as large arteries show the same proliferation of nuclei as was mentioned in the case of the arteries of the kidney.

The striped muscle fibres of the tongue, near the upper surface, show the interesting change that the nuclei of the muscle corpuscles have undergone a conspicuous proliferation, there being not only numerous examples of them in the state of division, or already divided into two or three, but—and this is of a very striking aspect—in many instances the proliferation has reached such an extent that long series of transparent small nuclei take their place (*see* Fig. XXII.), the number of these nuclei amounting from 10 to 30 and more. They are generally forming a lineal series along the longitudinal axis; occasionally, however, there is a small nest of them instead, or they form clusters at one or the other point of a series. A similar proliferation of nuclei is observable in the connective tissue sheath of the nerve branches.

With reference to the portion of the tongue, which, was converted into an opaque, hard mass, the whole tissue of the mucous membrane, as well as muscle, was filled with a fibrinous and granular matter, the original elements of the tissue, *e.g.*, epithelium connective-tissue fibres, nuclei and lymph corpuscles, muscle fibres, &c., having lost their outlines, and being transformed in some places into a débris-like mass.

At the root of the tongue the lymphatic follicles are very considerably enlarged, and many of them present a very peculiar appearance. Some of them, in stained sections which have not been shaken out, present the usual aspect of dense accumulations of roundish, deeply-stained nuclei; in others, however, only the peripheral part has retained this structure, whereas the greater or smaller portion of the centre is transparent and pale, showing few of the round and deeply-stained nuclei, in its greater part being composed of granular, flattened cell-masses of different sizes, and containing a variable number of transparent, sharply-outlined, oval nuclei. From cells with one such nucleus we pass to conspicuously large cell-plates, in the centre of which lie three, four, five, and up to 30 nuclei of the above description. The nuclei themselves are, like the cells, flattened, for when seen in profile, where they form a large collection, they appear like a narrow band composed of deeply-stained more or less staff-shaped bodies.

The epithelium of the folds and pits occurring at this part of the tongue, and also the epithelium of the mouth of mucous ducts, is much infiltrated with lymph corpuscles, the subepithelial adenoid tissue having at the same time grown into the epithelium to a greater or smaller extent. At the bottom of the folds there are distinct signs of proliferation of the nuclei of epithelial cells. At these places we find nests composed of concentrically-arranged layers of epithelial cells, the centre, which is of variable diameter, being formed by greenish blocks, which, as a comparative study teaches, are only epithelial cells that have become opaque and firm, having previously lost their nuclei.

The veins of this part of the tongue are much distended and filled with fibrin, in which are included very numerous colourless corpuscles. The lymphatic vessels are filled with colourless corpuscles.

The proliferation of the nuclei of unstriped muscle tissue of arteries,

and those of the muscle corpuscles of striped muscle fibres, is very conspicuous at the root of the tongue. In some of the nerve trunks of this portion of the tongue continuous homogeneous masses may be noticed within the sheath, which masses assume a bluish tint in preparations stained with hæmatoxylin; in unstained preparations they are not visible. It is probable that these masses are only some sort of albuminous exudation of an alkaline reaction.

Precisely the same appearances as in the root of tongue are to be met with in the tonsils, not only with reference to the epithelium of the mucous membrane, the endothelium and muscle tissue of blood-vessels, and the striped muscular tissue, but also with reference to the peculiar change of the central portion of lymph follicles, as mentioned before. There is a considerable amount of suppurative change and sloughing of swollen follicles in the depth of the tonsil.

The pharynx shows likewise inflammation, which is most intense next the tonsils, amounting, at those places, to ulceration. The further away the more the inflammatory symptoms decrease, *i.e.*, the less is to be seen of proliferation of nuclei of epithelial cells, infiltration with migrants of the epithelium and of the mucous membrane, changes in blood-vessels, and striped muscle tissue.

Case 4.—In this case we have precisely the same inflammatory appearances as in the preceding one, the changes at the root of the tongue in the tonsils and pharynx being of considerable intensity. In the tonsils there is sloughing in the depth and in the pharynx the mucous membrane appears under the microscope to be ulcerated over an extensive portion. In the root of the tongue, as well as in the tonsils, we find the same peculiar change of central part of some lymph follicles, being more transparent than the peripheral zone, containing only few round and deeply stained nuclei of ordinary lymph cells, and being chiefly composed of large flat cells with many nuclei.

In Fig. XXVII. I have represented this change as occurring in a lymphatic follicle of trachea, but as in the tongue and tonsil the change is identical, the figure may serve to illustrate what has been stated for the latter organs as well. I need hardly add that all the microscopic appearances of inflammation as detailed in the previous case, and referring to the condition of the epithelium, the mucosa, blood-vessels, nerves, and striped muscle tissue are precisely the same in both cases.

Case 5.—The tongue does not show so much inflammation as in the preceding cases, there being only moderate infiltration with lymph-corpuscles of the epithelium and the mucosa. As is usual the superficial layers of the epithelium are the parts which are most crowded with migrants, the residues of the epithelial cells forming a honeycomb, as it were, for the former. The papillae are much swollen, owing partly to the condition of the blood-vessels, and partly to the infiltration with lymph cells. The soft palate, which is much thickened, shows ulcerations of the mucosa of the upper surface, whereas the mucous membrane of the lower surface exhibits only a moderate amount of inflammation. The uvula is much swollen, and shows a considerable amount of inflammation.

The tonsils contain numerous small abscesses. We meet also here with lymph follicles changed so that, except a broader or narrower peripheral zone, the substance of the follicles has become transparent, being chiefly composed of large more or less flattened cells, with two, three, and more nuclei (multinuclear cells).

In this case the cells just mentioned have a distinctly yellowish tint under the microscope, which is very conspicuous in specimens stained

with haematoxylin, in which the unchanged peripheral portion of the follicles, containing closely aggregated small deeply-stained nuclei, is more or less distinctly blue.

Considerable inflammatory changes are observable in the mucous membrane of the pharynx, at some places the epithelium of the surface more or less destroyed by infiltration with lymph-cells.

Case 6.—The tongue shows much inflammation, the infiltration with lymph-cells of the epithelium covering the papillae is considerable at the basis, it decreases very much along the sides, and is very slight indeed at the apex.

In the root of the tongue many striped muscular fibres may be seen, the substance of which has become broken within the sarcolemma into several transverse blocks, parts of the striated substance disintegrating at the same time into granular matter. A similar desintegration may be observed in the striped muscle fibres of the uvula and pharynx. This latter is very much swollen, and shows under the microscope much oedema and a considerable amount of infiltration with lymph cells of the epithelium and mucosa, and chiefly of the tissue around the blood vessels. These latter are much distended and filled with blood, fibrin and colourless blood corpuscles.

The soft palate shows ulcerations of the mucosa of the upper surface, this latter being almost totally destroyed. The mucous membrane of the anterior surface is only moderately inflamed.

The tonsils show considerable sloughing of the enlarged lymph follicles.

The mucous membrane of the pharynx shows ulceration of the superficial and intense inflammation of the deeper parts. In the ulcerated parts of this organ, as well as of the soft palate of this and other cases, larger or smaller spherical or oblong or irregularly-shaped lumps of micrococci are found to penetrate from the surface into the depth for a greater or smaller extent. They are very easily traced by their peculiar purplish-blue colour these lumps assume in preparations stained in hæmatoxylin and by their resisting the action of caustic potash.

Case 9.—Inflammation of tongue is of moderate degree. Some arteries show distinct thickening of muscular coat, the nuclei of unstriped muscle fibres being in the state of proliferation. At the root of tongue lymph follicles much enlarged, many of them showing the transparent central part mentioned above. The same condition is found in the lymph follicles of tonsils, and in addition to this we find ulceration and sloughing of the superficial parts.

The soft palate and uvula show perhaps the most active inflammation, extensive parts being ulcerated. Moderate degree of inflammation is observed in the pharynx.

Case 11.—Considerable amount of inflammation of front part of tongue. Less so at the root. The soft palate shows ulceration of the mucous membrane of the upper surface, whereas that of the lower surface is not much inflamed.

The tonsil shows extensive sloughing of lymph follicles. It is not uninteresting to find in the depth of the organ sloughs in which are met with numbers of lumps of micrococci gradually displacing the disintegrating tissues. The blood-vessels of the adjacent parts are more or less plugged by fibrin, and some capillaries also by lumps of micrococci. These latter are easily recognized as blue lumps of uniform granulations. Caustic potash proves conclusively their vegetable nature.

In connexion with the tonsils of this case I must mention a fact to which I have already called attention, and which may be observed

in the other cases, both in the tonsils and at the root of the tongue: it is to the effect that the epithelium of the mucosa, penetrating as folds or cylinders or rounded masses into the depth of the organ, becomes gradually encroached on by the adjacent germinating adenoid tissue in such a way that that epithelium at first becomes crowded with lymph cells, then gradually replaced by the adenoid reticulum and lymph corpuscles, so that finally, apparently only the nuclei of the original epithelial cells are left. These (nuclei) have all the while been undergoing division. The inflammation of the pharynx is distinct, but not of an intensive degree. The lymphatics are very much distended by plasma.

Case 20.—The tongue is moderately inflamed. Of interest is the condition of the blood-vessels and nerves: the nuclei of the endothelium of arteries, veins, capillaries, and the nuclei of the sheath of nerve trunks are in a state of active germination, and many of them show transverse or longitudinal linear marks (*see* Fig. XXIV.). The number of nuclei of unstriped muscle fibres of arteries, as well as larger veins, is also much increased. The veins are distended and filled with fibrin and covered not only inside, but also outside, with colourless blood corpuscles. Some of the arterial vessels show the same hyaline degeneration of intima as mentioned in the kidney. In the rest of the organs of throat the usual appearances.

Case 22.—There is considerable inflammation of the mucous membrane at the root of tongue. Some of the enlarged lymph follicles show the central part transparent, and chiefly composed of large more or less yellowish tinted cells with large nuclei. The mucosa contains large coarsely granular migrants, which assume a deep blue colour in hæmatoxylin. The rest of the organs of throat show intensive inflammation, with the usual symptoms.

2. *Larynx and Trachea.*

Case 1.—The epithelium covering the epiglottis, and especially its posterior surface, shows much inflammatory change, and the superficial infiltrated layers are undergoing more or less desquamation. Near the free edge of the epiglottis the epithelium of the posterior side becoming gradually opaque, thinned, and raised from the mucosa, and finally altogether detached, so that a total defect of the epithelium on the posterior surface is found next the margin of the organ. The epithelium of the anterior surface shows much less inflammatory change, *i.e.*, proliferation of nuclei, infiltration with lymph-cells, and desquamation of superficial cells. The mucous membrane shows corresponding changes; that of the posterior surface is transformed into a firm, dense plaque of adenoid tissue, which here and there shows spherical or elliptical enlargements, that is to say, the lymphatic follicles of the posterior surface of the epiglottis have so much enlarged that they have become fused into one continuous plaque. The adenoid tissue decreases very much in amount near the margin, and is altogether absent in the mucosa of the anterior surface; in this latter there is infiltration with lymph cells only in the subepithelial layer. It is interesting to notice that the same change of lymph follicles that we observed in the root of tongue and tonsils is also to be observed in those of the posterior surface of the epiglottis, *i.e.*, the central portion being very transparent, owing to the disappearance of the ordinary small lymph-cells with deeply-stained circular nuclei, and the presence of transparent large multinuclear endothelial cells. The blood-vessels, and especially the lymphatics of anterior surface, very much distended.

The taste goblets of posterior surface very opaque, the individual cells indistinct. The whole goblet separated from the surrounding epithelium and mucosa by a clear space, *i.e.*, fluid.

The veins of posterior surface filled with fibrin. All the changes decrease in intensity towards the basis of the organ. The epithelium on the whole extent of both surfaces is laminated pavement epithelium.

The mucous membrane of the laryngeal entrance, *i.e.*, the false vocal chords, is covered with laminated pavement epithelium, more or less infiltrated with lymph cells. The mucosa contains numerous lymph corpuscles, amounting at many places to continuous masses of lymphatic tissue. In the ventriculus Morgagni the mucosa beneath the epithelium (ciliated columnar epithelium) is transformed into one plaque of lymphatic tissue, in which the individual lymph follicles are more or less distinctly defined. Some of the lymph follicles of the false vocal chords, as well as in the ventriculus Morgagni, show the central part transparent, *i.e.*, changed in the manner described above. The tissue around the mucous glands, and also the intermuscular tissue, much infiltrated with lymph cells.

The epithelium of true vocal chord is very much infiltrated just at the edge ; it is nearly normal in the adjoining parts, and becomes again much infiltrated lower down in the larynx. In the region of cricoid cartilage the superficial layers of the epithelium are just as intensely infiltrated with lymph cells as in the pharynx or root of tongue. The mucosa contains many lymph cells, and in the lower parts plaques of lymphatic tissue.

In the lowest part of larynx the inflammation is still more intensive. There is hardly any trace of the normal columnar ciliated epithelium, some places being covered either by a single layer of oblong cells, or, in addition to these, one, two, or more layers of polyhedral cells, between which lie smaller or larger numbers of lymph cells. At some places the epithelium looks just like laminated pavement epithelium, the superficial layers of which are infiltrated with lymph cells.

There is a hyaline elastic basement membrane of a considerable thickness immediately beneath the epithelium. Distinct canals pass from the lymph-lacunæ of the mucosa through the basement membrane into the canals and lacunæ of the epithelium (*see* Fig. XXI.). The mucous membrane of these parts is filled with lymph cells ; so is also the tissue around mucous glands, in some portions of which the nuclei of the lining epithelium appear to be increased in numbers.

The trachea shows in the upper parts very much the same kind of changes as met with in the lower portion of larynx, *i.e.*, the epithelium is at some places so changed from the ordinary laminated columnar epithelium that the superficial cells are polyhedral, or flattened ; at other places the epithelium so changed is densely infiltrated with migrants, the basement membrane thickened, and penetrated by canals. The is filled with adenoid tissue ; this reaches in some parts such an extent that the mucous glands of the submucous membrane have entirely or for the greater part given way before it. A similar change as that observed on the epithelium of the free surface may be noticed also on that of some large ducts of mucous glands. The ducts of some of these are exceedingly large, and lined near their mouth with laminated columnar epithelium, the most superficial cells of which are ciliated like those on the free surface. (Verson : article "Larynx," in Stricker's Handbook). Now, the epithelial lining of some of these ducts, surrounded by hypertrophied adenoid tissue, is over a greater or smaller area changed into laminated pavement epithelium, in which are

found smaller or larger cavities filled with migrants (*see* Fig. XXV. and its explanation).

Amongst the hypertrophied lymph-follicles are some which show the peculiar transformation of the central part containing large multinuclear cells (*see* Fig. XXVII.).

Blood-vessels are distended and filled with blood ; the nuclei of the muscular coat of arteries proliferating.

Case 4.—We shall be able to be very brief with this and the following cases, as we have described the general nature of the inflammatory changes of the larynx and trachea so extensively in the preceding case.

The changes of the epiglottis in this case are precisely the same as in Case 1, with regard to the inflammatory condition of the epithelium (including the epithelial defect near the free edge of the organ), and the hypertrophy of the adenoid tissue of the mucous membrane of posterior surface—in some parts, the mucous glands have been replaced by it to a smaller or larger extent. The mucous membrane of the anterior surface is more inflamed in this than in the former case.

The inflammation is likewise considerable in the mucous membrane of the larynx : false and true vocal chords and ventriculus Morgagni ; it is very slight in the lower region of the cavity of the larynx, and increases again somewhat in the upper part of trachea without, however, reaching the degree we noticed in the trachea of the previous case.

Case 5.—Epiglottis shows a considerable amount of inflammation ; epithelial defects near the free margin as well as near the basis, epithelium and mucosa in general much changed ; on the posterior surface lymphatic follicles very much hypertrophied and fused, so as to form continuous plaques.

The mucous membrane of the rest of larynx shows only slight though distinct signs of inflammation. Especially noteworthy is the fact that in some parts, *e.g.*, false vocal chords and lower region of larynx, *i.e.*, the region of cricoid cartilage, the mucous glands become entirely or to a greater or lesser extent lost as it were by the overgrowth of the lymphatic follicles of those parts. A similar state exists also in the trachea, in which the inflammation is otherwise only slight.

Case 6.—Epiglottis on both surfaces much inflamed. Epithelial defects on the posterior surface near the free margin of the organ. The lymphatic follicles of the posterior mucous membrane very much enlarged and fused into continuous masses. In some of them the greater transparency of the central part—containing the multinuclear large cells repeatedly mentioned—is conspicuous. The epithelial lining of some of the mucous ducts embedded in the lymphatic follicles of posterior surface contains larger or smaller cavities filled with migrants, similar to the cavities described in the epithelial lining of the mucous ducts of trachea of Case 1.

The mucous membrane of the cavity of larynx in general shows a moderate degree of inflammation. This becomes somewhat increased in the region of the first ring of the trachea ; here the epithelium has changed into laminated pavement epithelium more or less infiltrated with migrants ; the basement membrane appears much thickened, and the mucosa filled with numbers of lymph-cells. The same changes may be observed in the trachea ; in many parts the ciliated epithelium being completely replaced by laminated pavement epithelium; the superficial layers of the epithelium are infiltrated with lymph-corpuscles, and are in the state of being detached—desquamating ; the mucosa filled

with lymph-cells; these are found also in great numbers around the mucous glands.

Case 9.—Very intensive inflammation of the epiglottis, especially of the mucous membrane of the posterior surface : epithelium of this part altogether gone near the margin of the epiglottis, and also the superficial parts of mucosa at some points ulcerated. Great increase of lymph-follicles of the mucous membrane of the posterior surface. The mucous glands are in a state of destruction.

The inflammation is considerable also on the mucous membrane of the anterior surface. A similar condition is present in the mucous membrane of the false vocal chords.

In the rest of the larynx, the inflammation is considerable, and it is greatest just at the boundary of larynx and trachea, the epithelium at these parts being altogether destroyed through the intensity of the process. In the whole length of the trachea, the hyperæmia of the mucosa is very conspicuous, this (mucosa) being of a deep red-brown colour, owing not so much to the excessive distension and filling with blood of the superficial vessels as to the mucosa being soaked with blood colouring matter. The mucous glands are much infiltrated with lymph-corpuscles, their epithelium opaque and in some places breaking down. The lymphatic follicles enlarged.

Case 11.—Inflammation of epiglottis considerable, it is exceptionally more intensive on the anterior than on the posterior surface. The mucous membrane of the larynx in general shows inflammatory changes of no great intensity. The following facts are conspicuous; (*a*) the excessive thickening of the epithelial lining of the ducts of mucous glands, and also of the corresponding portions of the surface, the epithelium having changed in both places from columnar into pavement epithelium composed of very numerous layers. The epithelium of the ducts is not uniformly thickened, its layers being generally unequal on numbers of different sides of the wall, as is well seen in sections in which the duct is cut transversely as in Fig. XXVI.; (*b*) the basement membrane underneath the laminated pavement epithelium of the true vocal chord is swollen up into a bulky glassy mass, so is also the subjacent elastic tissue of the mucosa, having changed into a dense reticular mass of a hyaline tissue.

In the trachea, the inflammation is distinct, though only slight; it increases in intensity in the larger bronchi.

Case 20.—Moderate degree of inflammation of epiglottis, false vocal chords, ventriculus Morgagni and true vocal chords, comprising the ordinary changes of vessels, epithelium and mucosa. Immediately below the edge of the true vocal chords there is an extensive defect, ulceration of the superficial part of the mucosa; this contains great numbers of spherical or oblong lumps of micrococci penetrating for various extent into the depth of the mucosa. (They are easily recognized in preparations stained in hæmatoxylin by their being stained deeply blue, caustic potash leaves them untouched while dissolving all the rest). The tissue underneath the ulcerated surface is infiltrated with fibrinous material. It is of interest to notice that the epithelium of the mucous membrane of the larynx next the ulcerated part is changed from ciliated columnar into pavement epithelium consisting of a great number of layers ; the same is the case with the epithelial lining of the mucous ducts. In the latter it is very conspicuous. The same condition obtains very nearly up to the lower edge of larynx. The mucous membrane is slightly infiltrated with lymph-cells. The blood vessels distended and filled with blood and fibrin. The nuclei of the

endothelium of veins very markedly increased in numbers. The mucous membrane of the trachea shows very little change, the epithelium containing very numerous goblet cells filled with mucous.

Case 22.—The epiglottis shows very intensive inflammation, the superficial parts of the mucous membrane of both surfaces being ulcerated at many points. The mucous membrane down the larynx is slightly inflamed with regard to the epithelium and mucosa. The inflammation is most marked in the beginning of trachea, where the epithelium has so changed that it consists of several layers of polyhedral cells. The mucosa contains great masses of adenoid tissue. The mucous glands show, however, very little change. Lower down the mucous membrane is only slightly changed ; the epithelium contains very numerous goblet cells filled with mucous.

(B.) *General Remarks on the Changes of the Organs of the Throat.*

If we now summarise the results of the microscopic examination of the organs of the throat we arrive at the following conclusions :—

1. With reference to the tongue, palate, tonsils, and pharynx : in evidence of acute inflammation we have distended blood-vessels filled more or less with fibrin, leucocyte-infiltration of the mucosa, especially around the veins and capillaries ; leucocyte-infiltration of epithelium, particularly near the surface ; nuclei of epithelial cells in a state of germination, with their nucleoli in some instances exceedingly large, angular, double, or even multiple. On account of the presence of these changes the corresponding strata of epithelium become gradually transformed into a sort of honeycomb-structure, in which the outlines of the epithelial cells are indistinct or lost. At the same time it is to be observed that the more intense the leucocyte-infiltration of the superficial strata of the epithelium the more distinct is the exfoliation or peeling of those transformed layers.

The interstitial substance of the epithelium is very distinct, transparent, resembling broad clear canals, which at some places appear to have become distended to small lacunae ; through these canals or rather intercellular passages—they are probably only a fluid albuminous substance easily permeable both by fluid as well as formed parts—migratory cells find their way from the mucosa into the superficial layers of the epithelium. These interstitial canals are most marked on the fungiform papillae of tongue owing probably to the considerable swelling of these structures, attributable not so much to infiltration with lymph-cells as to exudation of plasma.

Then we have the proliferation of nuclei of the endothelium of blood-vessels, and likewise of the sheath of nerve-trunks, of muscular coat of arteries and the very conspicuous linear accumulation of nuclei in striped muscle fibres.

An interesting change is to be observed in some of the enlarged lymphatic follicles of the root of tongue and tonsils, consisting in the gradual disappearance of the ordinary small lymph corpuscles with their small circular deeply-stained nuclei from a greater or smaller portion of the centre—extending in most cases over more than half the diameter of a follicle—and the appearance of larger transparent cells with ovoid transparent nuclei. This gives to the follicle a very characteristic aspect ; the peripheral part which is composed of densely-crowded small lymph-cells with round deeply-stained nuclei appears in hæmatoxylin preparation of a deep purplish-blue colour, which contrast very conspicuously with the transparent only very slightly stained central portion. The

cells in in this latter are more or less granular, and of very different sizes; their outlines are never very distinct; they are, however, tolerably clear as long as they are small; when they have grown large they appear like flat transparent masses of very indefinite outline; their nuclei are as mentioned already, sharply defined, transparent, with one or more nucleoli, oblong or slightly irregular; the smaller cells have one nucleus, or a nucleus in state of division or already divided, or they have more than two nuclei; the largest cells have up to 30 and perhaps more nuclei. In some of the follicles the central part is composed only of large multinuclear cells, between which there are here and there a few of the smaller kind, and one or the other small lymph-cell.

Now the important question presents itself, what is the nature, origin, and fate of these cells? From the general character of these cells and their nuclei it is highly probable that they are endothelial elements, *i.e.*, flattened cells, with an ovoid transparent nucleus, which, as I have—in harmony with Bizzozero—pointed out in my paper on the Anatomy of Enteric Fever, (*see* these Reports, 1875,) in connexion with the lymphatic-follicles of the intestine, are placed on the adenoid reticulum, and are different from the lymph-corpuscles situated in the meshes of that reticulum. At the same time as the endothelial elements of the adenoid tissue increase in size, their nuclei undergo repeated division, and the ordinary lymph-cells of that tissue gradually disappear, until a condition is produced like the one represented in Fig. XXVII.

In some of the follicles it does not proceed to the formation of large multinuclear cells, for the enlarged endothelial elements having previously become slightly yellowish degenerate into a colloid substance, in other cases they change into fibrous masses. This we shall meet to a great extent in the cervical lymphatic glands, of which more hereafter.

In my paper on the Anatomy of Enteric Fever a similar change has been described of lymphatic follicles of the intestine, viz., the centre of some follicles becoming more transparent and showing chiefly enlarged endothelial cells, which are gradually transformed into multinuclear masses (*see* Fig. XLIV of that paper); in the case of typhoid fever these multinuclear masses were in some instances very regular "giant cells" of more or less cylindrical shape, the nuclei of which were chiefly distributed along the periphery (*see* Fig. XLV of the same paper). Like in the case of the lymphatic follicles of the intestine in enteric fever so also in that of the lymph follicles of the tongue and tonsils in scarlatina, there are apparently two kinds of processes going on, viz., one process in the course of which the overproduction of lymph cells leads to a destructive change, *i.e.*, to sloughing, suppuration, and another in the course of which the ordinary lymph cells disappear from a greater or smaller part of the follicles, and are replaced by large multinuclear cells derived from the pre-existing endothelial cells of the adenoid tissue. It is very probable that these cells show active changes only so long as their nutrition is not impaired either by mutual interference, *i.e.*, pressure in consequence of increased size, or by compression and obliteration of blood-vessels.

There is one more subject I wish to say a few words about. It is with reference to the ulceration of soft palate and pharynx and the suppuration and sloughing of the tonsils. It is an interesting fact that the ulceration of the soft palate is chiefly developed on the upper surface, and similarly also the pharynx when ulcerated is ulcerated chiefly in the part nearest the nasal cavity. With reference to the lumps of micrococci which we mentioned in connexion with the ulcerated parts of soft palate pharynx and tonsils, either of the following considera-

tions may suggest itself; (*a*) the micrococci may be of no other import than septic micrococci, which are thriving on an ulcerated surface, an occurrence not unknown in the pathology of ulcerations of mucous membrane; (*b*) or they may be indicative of diphtheria; or (*c*) they may be belonging to the proper scarlatinous affection. The second is not likely, for the reason that there were no diphtheritic membranes to be observed with the naked eye in any of the cases which I examined, the ulcerations being chiefly microscopic defects in an highly inflamed mucosa, whereas the first cannot easily be disproved, for the simple ground that the lumps of micrococci were found chiefly on the surface of the ulcerated parts, whence they extend into the adjacent parts which are in the act of breaking down. We mentioned their presence in the débris of a lymphatic follicle of the tonsil, which in the microscopic section appeared to be some distance from the surface, but it cannot be proved that those micrococci are not directly or indirectly connected with the free surface of the organ. If therefore on the one hand it appears probable that the lumps of micrococci found in the ulcerated and sloughing parts, connected with the free surface, have no specific significance, the possibility is not altogether excluded, that they stand in some connexion with the scarlatinous process. MacKendrick observed (British Medical Journal, 1875), micrococci on the mucous membrane of the inflamed throat in scarlatina, he is inclined to attribute to them a specific character. This I think cannot be done with safety so long as there is another and simpler explanation for their occurrence.

It is probable that all the morbid changes in scarlatina play an important part in the distribution of the contagion, no matter whether they arise in the skin, throat, lymphatic glands, or other organs, inasmuch as the morbid processes in these different organs are the result of the action of the specific virus. We have here specially in view the fact that the epithelium of all the organs of the throat, tongue, pharynx, palate, and, as we have seen, also the mucous membrane of the larynx and trachea, is charged with inflammatory products, and that its superficial layers, which in many parts are especially rich in those products, are being cast off in a smaller or larger quantity, not to speak of those parts where the tissue in consequence of suppurative changes is altogether breaking down into a débris. The contagiousness cannot be referred to the skin alone, for the desquamating epithelium of the skin and the material which is shed from the organs of throat are of one pathological category.

I tried a few experiments of inoculating guinea-pigs with the mucoproducts of the organs of the throat of Case 5, obtained very soon after death, but these experiments gave no other results than (in some cases) such as might be ascribed to common septic inoculation.

(2.) With reference to the larynx and trachea there is very little to be said different from what has been said with reference to the pharynx and palate. All parts of the larynx show inflammatory changes, which at some points—as epiglottis and lower margin of larynx—are more intensive than at others, amounting in some cases to ulceration; also the trachea is slightly inflamed. Besides the ordinary symptoms of inflammation, the following appearances deserve special notice: (*a.*) the changes of the epithelium in some parts of the larynx and trachea, the epithelium having, namely, changed from columnar and ciliated into laminated pavement epithelium, which may desquamate to a greater or smaller extent; in some parts the increase of the thickness of the epithelium of the surface as well as of that lining the ducts of mucous glands is very great; (*b.*) the hypertrophy of the adenoid tissue of the posterior

surface of epiglottis, false vocal chords, ventriculus Morgagni, and trachea; in some of the hypertrophied lymph follicles the same changes are observed as in those of root of tongue and tonsils, *i.e.*, the central part contains large multinuclear cells, very few ordinary lymph-cells, and is much more transparent as compared with the peripheral portion; (*c.*) the partial or total destruction of mucous glands by the hypertrophied lymphatic tissue; the epithelial lining of mucous ducts surrounded by lymphatic tissue shows distinct signs of proliferation, being at the same time penetrated by lymph-cells, which accumulate in small cavities.

V.—Examination of the Alimentary Canal.

Of the alimentary canal, the œsophagus has been examined in cases 1, 5, 6, 9, 11, 20, and 22; the stomach, the small and large intestine in Cases 9 and 11. To these I have to add the lower part of ileum that I had examined about two years ago of a case that died in a very early stage of scarlatina, I believe in the middle of the first week; the mucous membrane of the lower part of ileum of this case was studded with numerous whitish papules of the size of a millet seed.

1. *Œsophagus.*

The œsophagus was in all cases slightly inflamed: infiltration with lymph-cells of the subepithelial mucosa and the epithelium itself, and distension of blood-vessels. The inflammation is, as a rule, most marked in the upper part next the pharynx, but in some cases it is quite as intensive in the lower portion of the œsophagus as in the pharynx, *e.g.*, in Cases 6, 9, 11. The intensity of the inflammation varies in the different cases; whereas, for instance, in some cases, 5 and 20, the chief symptom of inflammation besides the condition of the blood vessels, is the infiltration of the sub-epithelial mucosa, the epithelium itself showing only slight changes—a few migrants amongst its cells. We find in other cases not only a very considerable infiltration of the mucosa with lymph-cells, but also very great numbers of migrants in the superficial layers of the epithelium, which at the same time shows signs of proliferation in the deeper layers, and distinct desquamation of its surface strata. In Cases 1, 9, 11, and 22 the inflammatory change amounts at some parts to partial or even total destruction of the epithelium, and to breaking down of the most superficial part of the mucosa—ulceration. The mucous glands situated in the submucous tissue appear little affected; only in Case 6 have I seen the epithelium of some parts of the glands opaque and swollen, or disintegrating into granular matter.

The walls of veins as well as arteries were distinctly thickened in Case 20 owing to an increase of the nuclei of the endothelium as well as of the muscle fibres.

2. *Stomach.*

In Case 9.—The stomach of this case was very well preserved. The following changes were observable: the epithelium was detached and gone from the surface of a few folds. The epithelium lining the gland tubes is in some instances found to be loosely attached to the membrana propria, and even becoming discontinuous. At the bottom of the gland tubes the epithelium is detached from the membrana propria, but the lumen of the tube is still distinctly preserved.

The tissue surrounding the basis of the glands is filled with very numerous lymph-cells, that is to say their number being much greater

than in the normal condition. In some of the large arteries of the submucous tissue the nuclei of the muscle fibres are distinctly proliferating.

In Case 11.—The epithelium of the surface and the ducts of glands is breaking up into small granular elements, the epithelial lining of the deeper parts of the gland-tubes is seen to be more or less detached from the membrana propria, and in some instances is breaking up into its elements. The veins and capillaries filled with blood. The nucleated septa extending from the membrana propria between the individual cells lining the gland tubes are very distinct, thick and deeply stained in logwood preparations. The tissue of the mucosa (between the gland tubes) is swollen up into hyaline structures. This last fact indicates that the wall of the stomach had probably been subject already to post-mortem digestion, and that therefore the condition of the epithelium of the surface and glands has probably not been existing during life.

My observation of the well-preserved stomach (Case 9) differs from the cases observed by Fenwick. This author says (l. c., p. 101) : "The first effects of the scarlatina poison upon the "stomach seem to be to congest the blood-vessels and to strip the "epithelium from the tubes and the surface of the organ, at the same "time that the tissues are softened. The tubes are greatly distended "with granular and fatty matters or with cells intermixed with granules ; "whilst in other cases they are lined by a newly-formed membrane. "Sometimes no normal cells can be distinguished, in other cases they "are present, but are scattered irregularly."

(3.) *Small and Large Intestine.*

In Case 9.—The duodenum shows the following changes: the epithelium covering the villi loosened or entirely detached, whereas that lining Leiberkühn's crypts is in many instances breaking up into the individual cells, which are for the most part transformed into goblet-cells. In Brunner's glands the epithelial cells lining the secreting parts are swollen and transparent ; in some tubes they are detached from the membrana propria, isolated, and lie scattered about all along the cavity of the tube, being at the same time transformed into goblet-cells each with a round transparent nucleus at the pointed extremity. In the ileum we meet with the same condition of the epithelium covering the villi as well as that lining Leiberkühn's crypts. The tissue of the mucosa between the crypts is increased in amount owing chiefly to the increased number of lymph-cells.

In the lower part of ileum the mucous membrane contains structures identical with lymph follicles, forming a nodular swelling projecting more or less over the free surface. [When looking at the internal surface of the ileum with the unaided eye those swellings were recognizable as smaller or larger papules raised slightly over the general surface of the mucosa—a condition very well known to pathologists.] In my paper on the Anatomy of Typhoid Fever (see these Reports, 1875, p. 91) I have pointed out that the papular swellings observable in the lower end of ileum in that form of the disease called by French writers "la forme bontonneuse" is not, as has been always supposed, due to hypertrophy of pre-existing solitary lymph-follicles, but only partly so, for a portion of them owe their origin merely to a local increase of the pre-existing adenoid tissue, of which the mucosa is composed. The same relation I maintain also for the papular swellings observed in the ileum of this case as well as of that other case which I mentioned in the commencement of this chapter as having been examined by me about two years

ago, viz., that some of them are due to a hypertrophy of solitary lymph follicles, others to that of the pre-existing adenoid tissue of the mucosa.

With regard to the cœcum we find: loosening and detachment of epithelium of the free surface, detachment from the membrana propria, and even breaking up of the epithelium lining Lieberkühn's crypts into small cells which are at the same time transformed into goblet-cells; the lymphatic follicles are enlarged, and show a transparent centre containing large transparent cells with one, two, or more oval transparent nuclei—a condition similar to that described of the lymphatic follicles of the organs of throat.

In Case 11.—The conditions prevailing here are much the same. In the duodenum we find: epithelium of many villi gone; where it is left its cells are either very opaque or they are transformed into goblet-cells; in some parts also the tissue of the villi appears to be breaking up. Dark pigment granules are found in the cells of the villi. The mucosa is much hypertrophied; the epithelium of Lieberkühn's crypts is very opaque and granular, many cells are goblet-cells, the lumen of the crypts is, however, distinct and empty. At the mouth of the crypts the epithelium is missing; the epithelium-cells lining the tubes of Brunner's glands are either goblet-cells or altogether gone, and in their stead the tube contains a slight amount of granular matter; the lymph follicles are much enlarged, all of them showing the transparent centre, containing large hydropic cells; the blood-vessels distended and filled with blood; the serous covering and the connective tissue in the external longitudinal muscle-coat is much swollen and almost hyaline.

In the ileum: the epithelium covering the top of villi is either raised and separated from the subjacent tissue by cavities containing cells and granular matter, or is altogether broken away. The epithelium lining Lieberkühn's crypts is not changed. In a few places there are swollen lymph follicles with transparent centre; the blood-vessels of the submucous tissue are filled with blood. In the lower part of the ileum the swelling of lymph follicles is very great, and the difference between a central and peripheral zone can readily be recognised with the unaided eye on preparations stained in hæmatoxylin: the increase in number of the nuclei of the endothelium in minute blood-vessels of these lymph follicles is very marked.

The condition of the cæcum and processus vermiformis is similar to that of the last-named case. Epithelium of the surface, and at the mouth of theLieberkühn's crypts is loosened, and in some places altogether missing; that lining the crypt itself is only slightly more granular, otherwise normal. The mucosa is more numerous in lymph cells than normally. The lymph-follicles are enlarged. In the processus vermiformis they show very well the transparent central portion.

Thus we find in the intestine in general changes due to slight degrees of catarrhal inflammation and œdema: loosening and breaking down of epithelium of different parts, and increase of cells of the mucosa, the lymphatic follicles of some parts (duodenum, ileum, and cœcum) are enlarged, and their central portion has undergone the same change as described in those of the throat, *i.e.*, disappearance of ordinary lymph cells from the central portion, and the presence of enlarged transparent cells with one, two, or more nuclei. The duodenum appears to be mostly affected.

Here again my cases do not quite tally with those of Fenwick, who found (l.c., p. 101) that "the effects of inflammation (sc. Scarlatina) "upon the intestine seems, in slighter degrees, to consist in the effusion of "granular and fatty matters into the mucous membrane; but in more

" severe cases the tubes of Lieberkühn are often choked with epithelial " cells, whilst extravasation of blood takes places in the villi; and these " with the rest of the mucous membrane are loaded with small cells " and granules. In one case the villi were completely destroyed, and " the tubes of Lieberkühn were greatly enlarged and distended by cells " and granular matter."

That the mucous membrane of stomach and different parts of intestine are sometimes affected with a much more or less distinct catarrhal inflammation, and that the lymphatic follicles are in some instances enlarged, is well known. *See* E. Wagner, l.c., and Thomas in Ziemssen's Cyclopædia, p. 227.

With reference to the lymphatic follicles of the intestine, John Harley, [The Pathology of Scarlatina &c., Medico, Chirurgical Transactions, second series, volume 37, 1872] has made extensive studies—40 cases—in their gross anatomical relation. He finds (p. 123 and 124): "The " solitary glands of ileum were forming white granular or papular solid " feeling elevations, giving the mucous membrane the appearance of " being thickly sprinkled with grains of sago in 14 cases. In others " the solitary glands were only partially affected, the swelling being " usually softer and more diffuse, and the glandulæ deeply injected." In four cases the glands were unaffected "The solitary glands of " large intestine were enlarged and inflamed in several cases. In one " of them there was acute desquamation of the mucous membrane " of nearly the whole of the large intestine. In another case the " cæcum was severely conjested." In half of the cases no alteration was to be observed in the solitary glands of large intestine.

" The agminated glands were more or less swollen and inflamed in " every case but one."

VI.—Examination of Salivary Gland, Pancreas Gland, and Liver.

The salivary gland (submaxillary gland) has been examined in Cases 5, 9, and 22; the pancreas in 9 and 11; whereas the liver had been studied in Cases 1, 4, 5, 6, 9, 11, 20 and 22.

1. *Salivary Gland.*

In Case 5.—The epithelium of small ducts detached from the membrana propria, the lining cells of most alveoli granular and their outlines not well marked. The most important change, however, is presented by collections of lymph cells in the connective tissue supporting the ducts and larger blood-vessels. They each possess one nucleus and form at some places not well-defined infiltrations, and are apparently in connexion with the large venous vessels. In some of the large ducts is contained the same kind of glistening amorphous or globular (lime) matter which we met with in the tubes of kidney in some of the above cases; in this case also it stains deeply blue in hæmatoxylin, and is soluble in dilute hydrochloric acid.

In Case 9.—The collection of lymph-cells in the lobular septa is very conspicuous, they are chiefly around veins. The lymph spaces in the lobules are very distinct, being in a distended condition. The blood-vessels are filled with blood. The nuclei of muscle fibres of arterial coat are in a state of proliferation.

In Case 22.—We find the same condition as in Case 5, with the addition that the collections of lymph-corpuscles in the connective tissue is not limited to the part around the veins, but appears to be connected also with the large ducts.

This condition, *i.e.* the collection of lymph cells in the connective tissue surrounding the veins and ducts, is to be regarded therefore probably as a constant feature, occurring as it does in cases of very different periods, as in Case 5, after an illness of four days' duration, in Case 9, five, and in Case 22, twenty-six days.

2. *Pancreas.*

In both cases—9 and 11—in which this gland had been examined the changes were found to be only slight, they are as follows: The epithelial lining of many alevoli detached from thier membrana propria, and in a few instances the epithelium was found breaking up into small nuclear granular elements, scattered irregularly through the cavity of the corresponding alveoli. The blood-vessels are distended, and the lymphatic vessels of the interlobular septa are very distinct. There are small collections of lymph corpuscles in the connective tissue around large ducts.

Fenwick (l.c.) also found the pancreas in a slightly inflamed condition.

The symptom of collections of lymph-corpuscles in the connective tissue around the larger veins and ducts, which we meet with so constantly and conspicuously in the salivary glands, and also to a certain extent in the pancreas, is still more highly developed in the liver, as is shown in the following cases.

3. *The Liver.*

Case 1.—The liver slightly enlarged. The liver cells in general granular, opaque, and swollen, so that their outlines are not very distinct. In some parts the liver cells are filled with small fat globules. The walls of intralobular capillary vessels opaque and granular, and between these and the trabeculæ of liver cells we find large granular flattened cells with an oblong clear nucleus. There can be little doubt about these being the enlarged intralobular connective-tissue cells. The chief feature of interest, however, is the presence of numerous lymphoid-corpuscles in the interlobular connective tissue. These cells are of two kinds; (*a*) ordinary round lymph cells generally with one round nucleus, in a few instances with two small nuclei staining deeply in hæmatoxylin; and (*b*) larger granular cells with a large ovoid clear nucleus and nucleolus. In some of the last-named cells the nucleus is divided or is in the act of division. These cells form more or less dense accumulations between the bundles of the interlobular connective tissue. The greater the number of these cells the thicker appear the interlobular septa. These cells are seen to be most numerous around the bile ducts. The collections of cells are in some places so numerous that they form continuous masses, and hence the interlobular tissue appears much thickened over larger or smaller sections of the liver. The adventitia of the very large bile ducts contains also numerous lymph cells, and the lining epithelium is infiltrated with small cells similar to colourless blood corpuscles; very often the epithelium is detached from the membrana propria and disintegrating. The last-named fact may be observed also in small bile ducts.

The arteries are distinctly thickened, the nuclei of their muscular coat increased in numbers; in some of them the intima at some points shows the same hyaline degeneration noticed in the kidney.

Case 4.—The following are the changes to be noticed in this case:—(*a.*) The liver cells next the central intra-lobular vein are opaque, they are smaller and their edges are rounded off, *i.e.*, they are loosely con-

nected with each other, some are even breaking up into granular fragments. In some places the liver-cells are filled with fat droplets. At some parts the intralobular lymphatic spaces, *i.e.*, those between liver-cells and capillary blood-vessels, are very marked, being distended, and the intralobular connective tissue cells lying in those spaces are like those in the preceding case, enlarged and granular. (*b.*) The nuclei of the muscular coat of arteries are much more numerous than under normal conditions, the interlobular veins contain much fibrin and numerous colourless corpuscles. The nuclei of the epithelium of minute bile ducts are more numerous than normally, and in some instances are seen in state of division. In some small bile ducts the epithelial lining is seen to be detached from the membrana propria. (*c.*) The interlobular connective tissue shows the same accumulation of cells as in the former case, and the infiltration with lymphoid cells is encroaching already on the periphery of the acini themselves.

Case 5.—In addition to the changes mentioned in Case 4 there is in this case thickening of the capsule of the liver at some places owing to the presence of numerous lymphoid corpuscles between its connective-tissues bundles.

Case 6.—The liver is slightly enlarged. The liver-cells next the central intralobular vein contain pigment granules. All the other changes are the same also in this case, viz., the changes referring to the liver cells, the intralobular lymph spaces, the intralobular connective-tissue cells, the blood-vessels and bile ducts and the cell accumulation in the interlobular connective tissue. This infiltration is very considerable, and is encroaching already on the peripheral parts of the liver acini.

Case 9.—The liver distinctly enlarged. The interlobular tissue is very much thickened over extensive portions of the liver, owing to the fact that the cell accumulations form continuous masses. The intralobular connective-tissue cells are very distinct and numerous, and besides them there are also a few small round lymph cells, so that we have at some places the same kind of cells as those in the interlobular tissue, viz., (*a.*) ordinary small round cells, and (*b.*) larger granular cells with an ovoid nucleus. All other changes are the same.

Case 11.—The cell-accumulation in the interlobular connective tissue is very slight in this case, but quite distinct. The liver-cells next the intralobular vein opaque, and in some instances filled with small fat-globules.

Case 20.—Considerable fatty infiltration of liver-cells in the peripheral portion of acini, whereas those near the intralobular vein are opaque, granular, and disintegrating into granular fragments. The interlobular connective tissue contains only small collections of lymph-cells.

Case 22.—The lymph spaces near the interlobular veins are very much distended, and the liver cells of the adjacent part opaque and smaller, their angles rounded off ; occasionally they contain pigment-granules. The cell accumulations in the interlobular connective tissue are distinct but not very numerous. Veins and capillary blood-vessels in general distended and filled with blood.

Thus we see that the liver presents in all cases, earlier as well as later stages, the same important changes. The abnormal condition of the liver cells and the state of the blood-vessels are evidently not of so great an importance as the alterations of the inter- and intralobular connective tissue. The first is thickened owing to the accumulation of lymph-cells forming more or less continuous masses. It is no doubt

interesting to find that already after two and five days' illness the liver should present such masses of interlobular cell accumulations, as happened in Case 1 and especially in Case 9. The cells are of two kinds: large and small ones. The large ones which we described as granular cells with a single or a double oval clear nucleus are no doubt merely the enlarged connective-tissue corpuscles of the interlobular connective tissue, whereas the small ones with a round nucleus staining deeply in hæmatoxylin correspond to the ordinary round lymph cell. When the interlobular cell accumulations are already encroaching on the peripheral portion of the acini, these latter contain in addition to the enlarged connective-tissue cells also a few round cells.

It appears that in the later stages, Cases 11, 20, and 22, the cell-accumulation in the interlobular tissue is decidedly much slighter than in the earlier stages, and that also the changes of the liver cells are more marked in the later stages, thus proving that they are not dependent upon the interlobular condition.

This is what I find in the literature with regard to the interlobular cell-accumulation: E. Wagner (l.c.) found in the same case that was quoted on a previous page (*see* Kidney), *i.e.*, a case in which death ensued after 48 hours, the following conditions of the liver: the organ was of normal size, on its anterior edge were visible (with the unaided eye) numerous, on other places few very minute whitish granules; the same is observable on all cut surfaces of the liver. Under the microscope these white masses were seen to represent the same kind of new growth of lymphatic or adenoid tissue, which E. Wagner found in the liver and spleen in some cases of variola (Archiv der Heilkunde, V. Jahrgang, p. 90. The cells and nuclei representing that new growth were chiefly situated in the interacinous connective tissue, which appeared therefore much thickened. The liver of the scarlatina case contained "besides the microscopic "whitish masses, in addition numerous microscopic groups of cells "and nuclei, chiefly in the interacinous connective tissue. The liver "cells were nearly of normal size, but much clouded by albuminous "and fatty molecules."

In a second case of scarlatina,—boy of three years,—who died after 23 days in consequence of diphtheria, E. Wagner found the same condition of the liver, which was, however, distinctly enlarged.

In the case published by Biermer (l.c.) the liver was enlarged, and showed on microscopic examination "a very distinct meshwork of connec-"tive tissue with a few nuclei, in which the liver-cells were embedded. "The central portion of the acini surrounding a vein, the wall of which "is likewise somewhat richer in connective tissue, are yellow, owing "to a very marked accumulation of fat in the shape of smaller and "larger droplets, whereas more peripherally the cells are pale without "granular content, and are embedded in an increased connective tissue "network."

Although in this description of Biermer there is an increase of connective tissue undoubtedly to be recognised, still it is not of the same character as that in the two cases of E. Wagner. If I am to judge by my own cases I should be inclined to think that the new formation of cellular tissue is, as a rule, only distinct in the earlier stages of scarlatina, in later stages the cellular nature becoming more indistinct, the hypertrophied tissue having the character of fibrous connective tissue, as in the case of Biermer.

VII.—Examination of Lymphatic Glands.

The following lymphatic glands were examined:—

(*a.*) The lymphatic glands of the neck of Cases 1, 4, 5, 6, 9, 11, 20, and 22; (*b.*) the mesenteric glands of Cases 9, 11; (*c.*) the bronchial lymphatic glands of Case 11.

All these glands were considerably enlarged and hyperæmic. Those of the neck of course most, but in no case was there any suppuration in them.

(*a.*) The lymphatic glands of the neck.

Case 1. The follicles and follicular cylinders are very much enlarged and their lymph cells easily shaken out; the fibres of the adenoid reticulum increased in thickness, and very many of the lymph cells of the adenoid tissue, as well as in the lymph sinuses are enlarged and possess a transparent vesicular nucleus unlike that of the ordinary lymph cells, which stains uniformly and deeply in staining fluids. The lymph sinuses of the medulla contain numerous cells of very various aspect and sizes, from ordinary small lymph cells, with one round nucleus deeply staining in staining fluids up to large granular or transparent cells, with one or two oval transparent nuclei. In the cortical lymph follicles the contrast between the ordinary lymph cells and the enlarged endothelial cells (see what has been said of lymph follicles in the organs of throat) is very conspicuous. (Compare Fig. XXIII.)

Some of the cortical lymph follicles show the same change of their central portion that has been mentioned repeatedly on former occasions, *i.e.*, the disappearance of the ordinary small lymph cells from the central parts in which are present large granular cells with proliferating nuclei.

The blood-vessels are excessively distended, and many veins filled with fibrin. In the cortex the blood-vessels are all filled with blood.

The capsule and the connective tissue trabeculæ of the cortex are thickened by lymph cells, present in large numbers in them.

In some parts the cortical sinuses, and also at some points the peripheral portion of cortical lymph follicles are filled with what appears to be disintegrated cells, fibrin and granular matter.

Case 4.—The appearances are precisely the same as in the preceding case, with this addition, that the lymph sinuses of cortex, and especially of the medulla, are much distended by large lymph cells,—some of them vacuolated,—are filled with granular matter and fibrin. The thickened fibres of the adenoid reticulum, the enlarged lymph corpuscles, and the enlarged endothelial cells of the adenoid tissue, as well as the condition of the blood-vessels and the capsule, are the same as in the previous case. Numerous lymph follicles with transparent central portion.

Case 5.—The fibres of the adenoid reticulum are much thicker than normally; there are very numerous granular large endothelial-like cells in the cortical, and especially in the medullary lymph sinuses. In some portions they have become vacuolated. The blood-vessels are very distended, and in the cortical part they are filled with fibrin. The capsule and the trabeculæ are in many places much thickened by the presence of lymph corpuscles. The most important changes, however, are these: (*a*) there are follicles in which the central part has become transparent owing to the presence of enlarged cells; these in some places may be traced directly into huge granular giant cells, *i.e.*, masses of spherical or oblong shape, with a great number—20, 30, and more—of small transparent nuclei, in this case chiefly disposed in the periphery of the cell substance (*see* Figs. XXVIII., XXX., and XXXI.), or they may

be seen to become very hard in their outlines, and assuming a more or less fibrillar character; (*b*) larger or smaller masses of a rigid fibrous tissue are found to take the place of the adenoid structure with nucleated remnants between them (*see* Fig. XXVIII. and XXIX.). The fibrous masses owe their origin in the first place to the swollen trabeculæ of the adenoid reticulum which afterwards become transformed into fibrous bands, both the lymph corpuscles between them and the enlarged endothelial plates fixed on them becoming gradually involved in the same fibrous degeneration. There can be little doubt that some of the larger giant cells give rise to smaller ones, as in Fig. XXVIII., but what eventually becomes of them, whether they also undergo fibrous degeneration or not, I am not in a position to say. A rather curious appearance is presented in a preparation which is copied in Fig. XXIX., viz., the presence of a huge giant cell situated in a focus of fibrous degeneration, in some parts of which the outlines of the enlarged cells are still visible; the giant cell is surrounded, as it were, by a thick hyaline glistening capsule. This cell is represented separately in Fig. XXX. as seen under a higher power; what appears as the capsule is seen to extend in the form of processes into the vicinity. It seems to me probably that what appears as the hyaline and glistening capsule (the fibrillation of it in the drawing is not natural, but is due chiefly to the defective execution) is not a capsule surrounding the giant cell, but is merely a part of the original adenoid reticulum greatly swollen up.

In Cases 6, 9, *and* 11 we meet with precisely the same changes as those described in Case 4.

Case 20.—Besides general enlargement of the adenoid tissue including the usual thickening of the fibres and the enlargement of the endothelial cells of the adenoid reticulum, the distension and filling of the lymph sinuses with various sized cells—some of them being vacuolated—the distended blood-vessels and the thickened capsule and trabeculæ, we find as in Case 5, the following changes: (*a.*) Transformation of the central portion of some lymph follicles into a transparent mass owing to the presence of enlarged cells; (*b.*) in some places this leads to the formation of huge multinuclear giant-cells; (*c.*) in others they degenerate, together with the adenoid reticulum of the neighbouring parts into a firm fibrous material, having swollen up previously into a hyaline mass. I have seen in several instances in the centre of the smaller, *i.e.*, younger foci of fibrous degeneration what appears to me to be a distended vein blocked up by a dense mass of fibrin and lymph cells.

Case 22.—This case differs from the preceding one in the following points: (*a.*) great increase of connective tissue in the capsule and trabeculæ; and (*b.*) the absence of giant-cells in those portions of the follicular tissue that have undergone fibrous degeneration. Otherwise the appearances are similar. Small masses of pigment are found in the tissue of the capsule and cortical lymph follicles.

Thus we may say that the enlargement of the lymphatic glands of the neck is due to an inflammatory increase of all the constituent parts of the gland,—including the filling and distension of the lymph sinuses with large cells and granular matter, which no doubt have been carried into the glands from the inflamed throat organs—and to the change of the lymphatic follicles noticed also in other organs (throat and intestine) which, however, in the case of the lymphatic glands under consideration leads to the formation of true giant-cells and to fibrous degeneration of the corresponding parts of the adenoid tissue. It is probable from the observations of Case 22 that also the giant cells become involved in the fibrous degeneration.

(*b.*) The mesenteric glands of Cases 9 and 11 were of precisely the same appearance. They were enlarged and showed the same structural changes as the glands of the neck, viz. thickened capsule and trabeculæ owing to the presence of lymph cells, distended blood-vessels, in many of them masses of fibrin. In the minute vessels the endothelial nuclei are distinctly increased in number. Lymph follicles and follicular cylinders much enlarged, the fibres of the reticulum thickened, and the endothelial cells much larger; the lymph sinuses are filled with cells of various sizes and their nuclei in state of division. There are lymph follicles in which the central portion has become changed into the transparent tissue composed of enlarged cells, and the same appearance may be noticed also in many lymphatic cylinders of the medulla.

(*c.*) The bronchial lymphatic glands, as well as those along the trachea of Case 11, were much enlarged and presented the usual appearances, including the peculiar change—transparent large and multinuclear cells —of the central portion of some lymphatic follicles; and in addition to this the lymph sinuses of some portions of the gland are greatly distended by clear plasma, in hardened specimens a very finely granular transparent material.

John Harley (l.c.) found the mesenteric glands generally and severely inflamed, the whole mesentery being thickened and the glands purple and swollen, in some cases to the size of a pigeon's egg; and Thomas (l.c. p. 227) states that "the mesenteric glands are 'generally found " hyperæmic and some of them considerably swollen and, when cut " into, their tissue is found to contain more fluid than usual."

VIII.—Examination of the Spleen.

The spleen was examined in Cases 1, 4, 5, 6, 9, 11, 20 and 22. The organ appeared slightly enlarged only in cases, 4, 6, 11, and 22.

Case 1.—The Malpighian corpuscles and the adenoid sheaths of arteries are very distinctly enlarged. The former show in many instances the peculiar change of the central part, containing large endothelial-like cells. Another noteworthy change consists in the hyaline degeneration of smaller or larger portions of the intima of arteries, leading at some places almost to total obliteration and degeneration of the wall of the vessel. In connexion with these changes we find the swelling up of larger or smaller portions of adenoid tissue around those arteries into hyaline or slightly granular masses, fibres and cells being completely lost in the said masses. There are, however, arteries in which the nuclei of the endothelium as well as those of the muscular coat, have undergone distinct proliferation. The walls of the large veins are much thickened by the presence of cell masses next the endothelial lining, which masses look exactly like adenoid tissue.

Case. 4.—The most interesting features in this case are the Malpighian corpuscles; not only are they much enlarged (as well as the adenoid sheaths of arteries in general) but they present, in preparations stained with hæmatoxylin, a very curious aspect when looked at with the unaided eye, or better with a lens. Each Malpighian corpuscle besides being enlarged appears to be composed of three distinct zones (*See* Fig. XXXV); (*a.*) a transparent yellowish centre; (*b.*) a deeply stained middle; and (*c.*) a slightly stained peripheral zone, gradually shading off into the surrounding parts. When examined with a low power the threee zones exhibit the following conditions:

(*a.*) The central transparent zone is, I need hardly say, due to the absence of ordinary lymph cells with the small deeply stained nuclei, and in their stead we find only large cells, with one or more transparent

nuclei, a condition with which we are quite familiar by this time. Most of these cells are slightly tinged yellow, owing to their containing several smaller or one large yellowish colloid-like droplet. (By contrast with the blue-stained median zone the central part appears only the more of a distinctly yellow colour.)

(*b.*) The median deeply blue stained region shows ordinary small lymph corpuscles, each with a small circular nucleus deeply stained, on account of the smallness of the cells and therefore close aggregation of the nuclei, this region appears very deeply stained.

(*c.*) The peripheral zone is less deeply stained than the preceding one and is composed of lymph cells each with one nucleus, but on account of the cells themselves being larger than those of zone (*b.*) the nuclei appear further apart from each other, and hence this zone is less stained than (*b*). In Fig. XXXVI a small portion of the central and the median zone has been copied, under a moderately high power (Hartnack's Objective 5). The wall of large veins thickened by what appears to be adenoid tissue, in the same manner as in the former case. Many arteries show the hyaline degeneration of the intima.

Case 5.—The same changes may be observed also in this case, with the difference only, that there are not so many arteries showing the hyaline degeneration as in the former case, and the Malpighian corpuscles are not so much enlarged, and their central portion not being degenerated so distinctly as in the former case.

Case 6.—This case is still more marked than Case 4, as regards the degeneration of arteries, the hyaline and granular degeneration of adenoid tissue and to the hypertrophy and change of Malpighian corpuscles, viz., as if composed of three zones. The degeneration of adenoid tissue, lymph cells and reticulum, mentioned in previous cases, is here seen to take place in connexion with the changed Malpighian corpuscles. The wall of large veins thickened.

Case 9.—The same changes, only of a slighter degree.

Case 11.—All the appearances previously mentioned are very well marked.

Case 20.—The number of arteries showing hyaline degeneration of intima, and the number of places where also the adenoid tissue is swollen up into a hyaline or granular degenerated substance, is considerable ; so is also the thickening of the wall of the large veins.

Case 22.—The hyaline degeneration of intima of arteries may be observed in most arteries ; in some instances the vessel appears quite obliterated, its whole wall having degenerated into a fibrous looking substance. The thickening of the wall of large veins by the presence of cellular tissue—very much like adenoid tissue—is greater than in any of the previous cases. The Malpighian corpuscles and adenoid sheaths of arteries are hypertrophied, the former showing the change of their central portion. Considerable masses of adenoid tissue have undergone the hyaline degeneration.

Thus we find, in the spleen of all the cases examined, the same changes occurring constantly, namely : enlargement of adenoid sheaths of arteries and of Malpighian corpuscles, and peculiar change of the centre of the latter ; degeneration of arteries, and in connexion with it degeneration of the surrounding adenoid tissue ; thickening of the wall of large veins, owing to the presence, underneath the endothelial lining, of cell accumulations very much resembling adenoid tissue. With reference to the above changes, their intensity stands, so it

appears, in no relation to the stage of the disease, except in respect to the degenerative changes of the arteries, which in the later cases, 20 and 22, are undoubtedly more marked than in the earlier ones.

I need hardly add that the change of the Malpighian corpuscles is almost identical, at any rate of the same nature as the changes of the lymph follicles that we observed in the organs of the throat, and especially in those of the lymphatic glands; and likewise that the degeneration of adenoid tissue in the spleen is no doubt analogous to that observed in the lymphatic glands.

E. Wagner (l. c.) found the hypertrophy of the adenoid tissue in the spleen in both his cases, and Biermer (l. c.) found in his case the enlargement of Malpighian corpuscles very marked; "their constituent "elements, however, show no alteration."

EXPLANATION OF PLATES OF Dr. E. KLEIN'S REPORT.

Fig. I.—From a vertical section through epidermis of skin of case 2. Hartnack Ocular II., Obj. 5.

a. Rete Malpighii.
b. Stratum lucidum much thickened, and showing "granulation."
c. Stratum corneum.

Fig. II.—From Case 1. II., 7.

a. Rete Malpighii.
b. Cavity underneath the stratum corneum.
c. Filled with "granular" matter (*see* text).

Fig. III.—From a vertical section through epidermis of Case 18. (Desquamation) II., 8.

a. Rete Malpighii.
b. Stratum lucidum.
c. Stratum corneum.
d and *e*. "Granulation" contained in the desquamating parts. The lower edge of the "granular" lump, *d* is represented in the figure far too sharply.
f. Continuation of rete Malpighii on a sweat-duct.

Fig. IV.—Longitudinal view of a hair-follicle near its mouth, from Case 19. II., 7.

a. External root sheath.
b. Hair shaft.
c. Epidermis scales.
d. Thickened internal root sheath, containing "granulation."

Fig. V.—A similar preparation as Fig. IV. of the same case. II., 7. The meaning of letters the same as in IV.

e. Nuclei deeply stained.

Fig. VI.—From a preparation of kidney of Case 5. III., 9.

a. Arteriole in transverse section, most of the intima is swollen up into a hyaline mass, the nuclei of the muscular coat proliferating.
b. Section through a urinary tube (ascending tube of Henle), the nuclei of whose epithelium is much proliferating on the side nearest the arteriole.

Fig. VII.—From a similar preparation as Fig. VI.

a. Part of a glomerulus of Malpighian corpuscle.
b. Point of entrance of afferent arteriole into the glomerulus; the nuclei of artery much multiplied, and the intima in parts swollen up into hyaline blocks.
c. The urinary tube whose epithelial nuclei are much proliferating on one side.
d. Part of convoluted tubes.

Figs. VIII. and IX.—Malpighian corpuscles in process of degeneration into a hyaline or slightly striated substance.

a. Lumen of afferent arteriole.
b. Degenerated glomerulus.
c. Nuclei.
d. Thickened capsule.

Fig. VIII.—Is from Case 12, and drawn with II., 10, à immersion.

Fig. IX.—From Case 17, and drawn with II. 8.

Fig. X.—From kidney of Case 12. II., 7.

a. Afferent arteriole.
b. A portion of degenerated wall of the arteriole sliced off as it were, the artery having become at this point bulged out.
c. Point of entrance into glomerulus.
d. Glomerulus; nuclei of it much increased.
e. Bowman's capsule.
f. Convoluted tubes in section.

Fig. XI.—A Malpighian corpuscle greatly degenerated, from the kidney of Case 1. III., 7.

a. Lobules of glomerulus changed into hyaline masses containing nuclei.
b. Afferent arteriole.
c. Portion of glomerulus less changed than *a.*
d. Thickened and swollen capsule.

Fig. XII.—Degenerated Malpighian corpuscle, kidney of Case 12. III., 9.

a. Afferent arteriole, its wall much thickened.
b. Malpighian corpuscle.
c. Convoluted tubes in section.
d. Henle's tube.

Fig. XIII.—From the kidney of Case 17. II., 5.

a. and *b.* Degenerated Malpighian corpuscles.
c. Infiltration due to interstitial nephritis.
d. Urinary tubes in section.

Fig. XIV.—Malpighian corpuscle from the kidney of Case 18. H. II., 8.

a. Afferent arteriole containing an embolus; just at the point where the arteriole enters the glomerulus we find great increase of the nuclei of the artery's wall.
b. Space between Bowman's capsule and glomerulus; a few lymph corpuscles in it.
c. Infiltration with lymph corpuscles around the Malpighian corpuscle, and extending between the urinary tubes *d.*

Fig. XV. From a similar preparation of the same kidney. II., 5.

a. Interlobular artery, containing an embolus *e.*
b. Urinary tubes.
c. The same more or less filled with lymph-cells.
d. Malpighian corpuscle more or less degenerated. The tissue of this part much infiltrated owing to interstitial nephritis.

Fig. XVI.—From a vertical section through the kidney of Case 16. II., 5.

a. Large arterial, *v* large venous trunk at the boundary between cortical and medullary portion.
b. Convoluted tubes in section.
c. and *d.* Straight tubes of medullary rays.
i. Infiltration, *i.e.*, interstitial nephritis.

Fig. XVII.—From the kidney of Case 22. III., 7.

Portions of convoluted tubes, showing in 1 slight granular disintegration; in 2, fatty degeneration of epithelium.

Fig. XVIII.—Transverse section through small artery of epiglottis of Case 1. III., 7.

a. Lumen of artery.
b. Thickened muscular coat, showing in some parts multiplication of nuclei in muscle fibres.
c. Thin adventitia.

Fig. XIX. From a section through epithelium of a papilla of tongue, showing the intercellular canals, and migratory cells in them. III., 8.

a. Intercellular canals containing migrants.
b. Epithelial cells.

Fig. XX.—From a preparation of tongue, showing the infiltration of superficial layers of epithelium with lymph-cells, and division of nuclei of epithelial cells. III., 7.

Fig. XXI.—From a section through trachea; the ciliated columnar epithelium is replaced by layers of polyhedral cells. III., 8.

a. Basement membrane; through it pass fine lymph-canals, which lead into distended interepithelial spaces *b.*, some of which contain migrants.
c. Migrants among the superficial epithelial cells.
d. Epithelial cells.

Fig. XXII.—From a section through tongue; showing the multiplication of nuclei of striped muscle fibres. III., 8.

Fig. XXIII.—From a section through tonsil; showing the multiplication of nuclei of unstriped muscle fibres of coat of a large artery. III., 8.

Fig. XXIV.—From a preparation of tongue; showing the multiplication of nuclei of endothelial wall of a distended vein. III., 7.

Fig. XXV. From a section through trachea; showing the epithelium of a large duct of a mucous gland; the columnar epithelial lining of a part of the duct is replaced by polyhedral epithelium, in which cavities have been formed of different sizes containing migrants. II., 7.

a. Epithelial lining of duct.
b. Cavities in the epithelium containing lymph-cells.

Fig. XXVI.—Transverse section through the duct of a mucous gland of false vocal chord, showing the great thickening of the epithelial lining. II., 5.

a. Lumen of duct lined by a layer of columnar cells; this is surrounded by several layers of polyhedral cells, among them a few (deeply stained) migrants.

Fig. XXVII.—From a section through trachea; showing a lymphatic follicle changed in such a way that the central part shows only large granular multinuclear cell-masses; the periphery is composed of the ordinary masses of lymph-cells, whose number is, however, increased. II., 7.

Fig. XXVIII.—Giant-cells from lymphatic gland of neck; below *a.* the tissue is converted into a fibrous-looking material, including a few remnants of nuclei. III. 8.

Fig. XXIX.—Hyaline and fibrous degeneration of follicular tissue of lymphatic gland of neck.

a. A giant cell surrounded by a thick glistening homogeneous capsule. Round the giant cell are large swollen homogeneous or striated cellular masses. II., 7.
b. The tissue is already fibrous.
c. Lymphatic tissue of periphery.

Fig. XXX.—The giant cell of preceding figure more highly magnified III., 8.

a. Substance of giant cell finely and uniformly granular.
b. Hyaline capsule with two band-like processes, into which extends also the substance of the giant cell. The nuclei are situated in the peripheral part of the cell.

Fig. XXXI.—A giant cell of a lymphatic gland of neck. III., 8.

Fig. XXXII.—From a section through the cortex of lymphatic gland of neck (section had been shaken). III., 7.

a. Capsule of gland.
b. Cortical lymph sinus.
c. Lymphatic follicle.
d. Capillary blood-vessel.
e. Lymph-cells.
f. Large endothelial-like cells.

Figs. XXXIII. and XXXIV.—Arteries from spleen: showing the homogeneous swelling of intima. III. 5.

Fig. XXXV.—Malpighian corpuscle of spleen; showing three distinct zones.

a. Central part transparent, composed of swollen cells.
b. Intermediate zone, deeply stained in hæmatoxylin, because composed of dense accumulation of small nuclei of ordinary lymph-cells; and
c. Peripheral zone less deeply stained than *b.*, because composed of larger lymph-cells, the nuclei therefore less densely accumulated. II., 4.

Fig. XXXVI.—Showing a portion of *a.* central, and *b.* intermediate zone of Malpighian corpuscle under a higher power than in the preceding figure. III., 5.

Fig. XXXVII.—From the kidney of Case 21. III., 5.

a. Interlobular artery.
b. Infiltration due to interstitial nephritis.
c. An afferent arteriole degenerated.
d. Outlines of urinary tubes.

Fig. XXXVIII.—From the kidney of Case 19. II., 7.

a. Artery in transverse section, its muscular coat much thickened.
b. Sheath of artery completely resembling adenoid tissue.
c. Outlines of urinary tubes.

Fig. XXXIX.—Henle's tube from near the papilla in 1, the epithelial cells detached from membrana propria, large and granular, and containing lime-elements. In 2 it is still better seen that these last-named are contained within the epithelial lining. III., 8.

Fig. XL.—Interlobular infiltration of liver of Case 1. III., 4.

a. Bile duct.
b. Arteries, their wall much thickened.
v. Vein.
c. Lymph-corpuscles in the connective tissue; they are of two kinds: small deeply stained nuclei, and larger cells, the nuclei of which are large, transparent, oval or rounded.

Fig. I

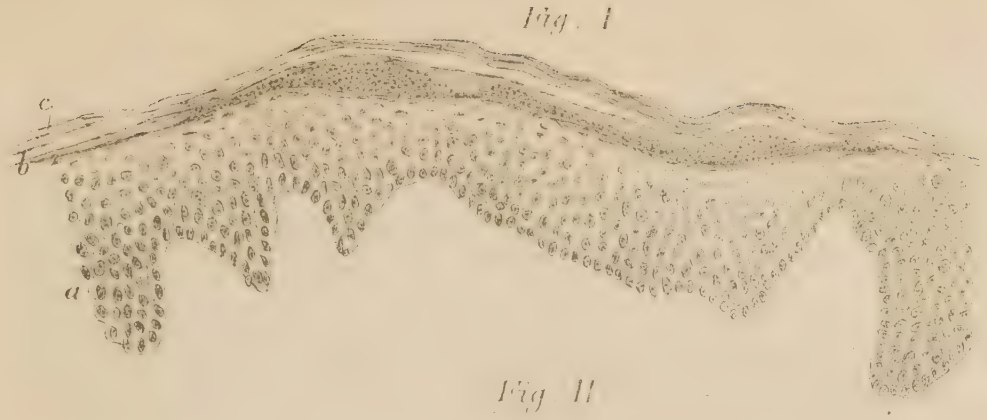

Fig. II

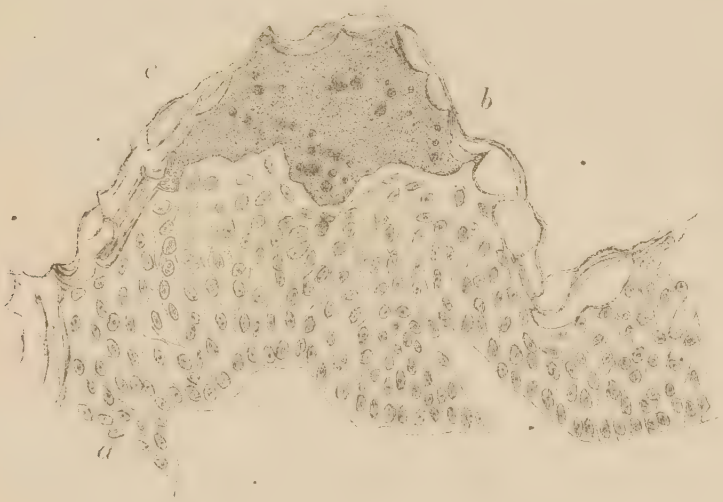

Fig. III

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Fig. VIII.

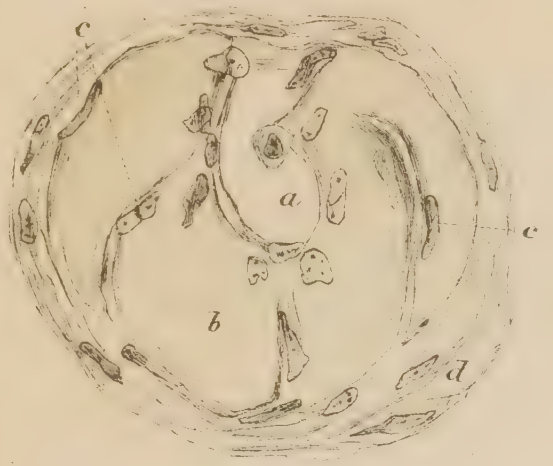

Fig. IX.

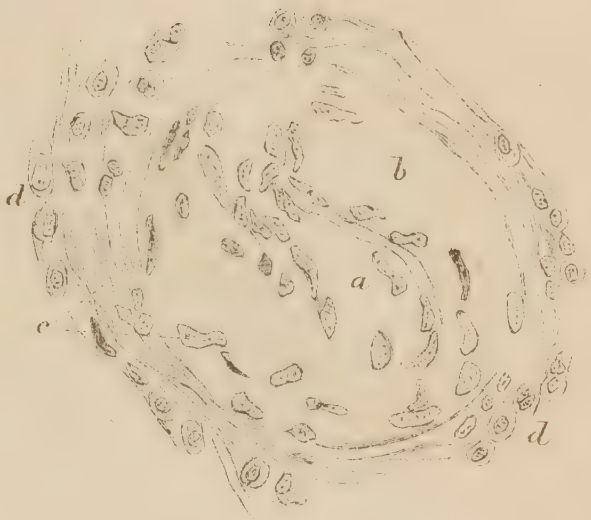

Fig. X

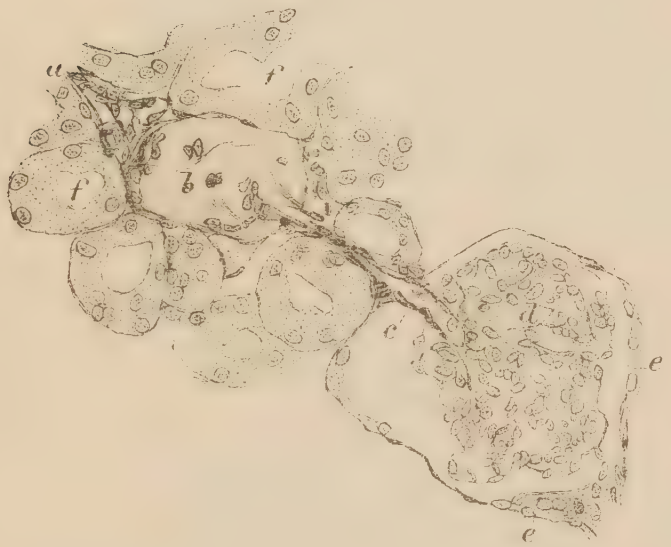

Fig. XI.

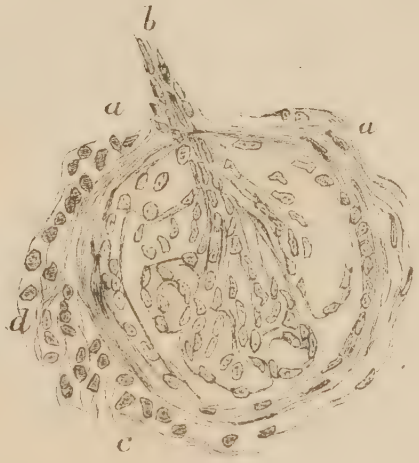

Fig. XII.

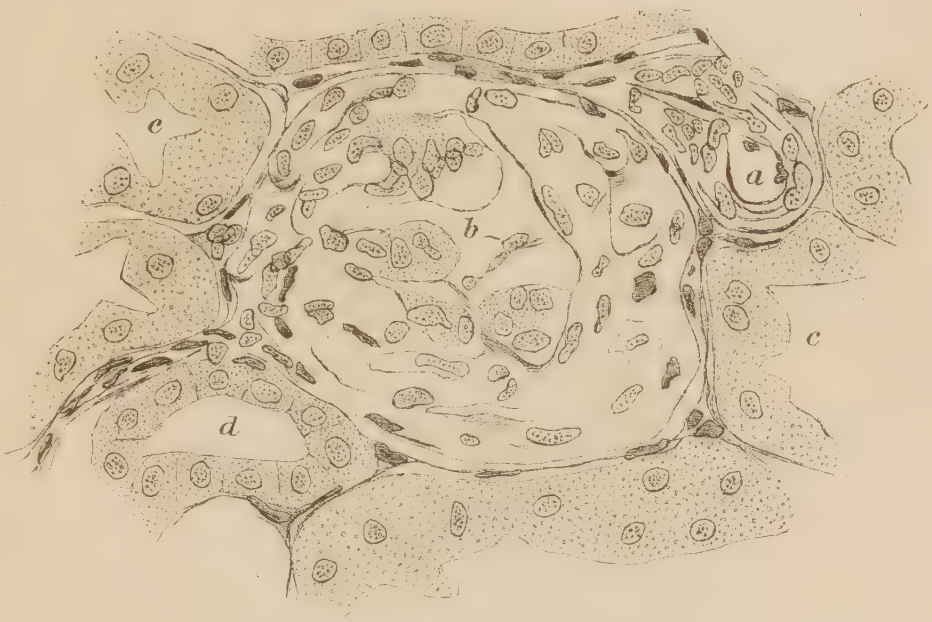

Fig. XIII.

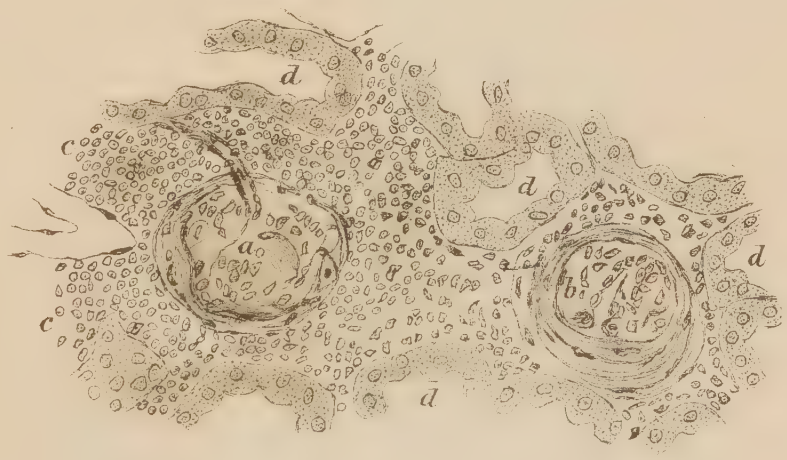

Fig. XIV.

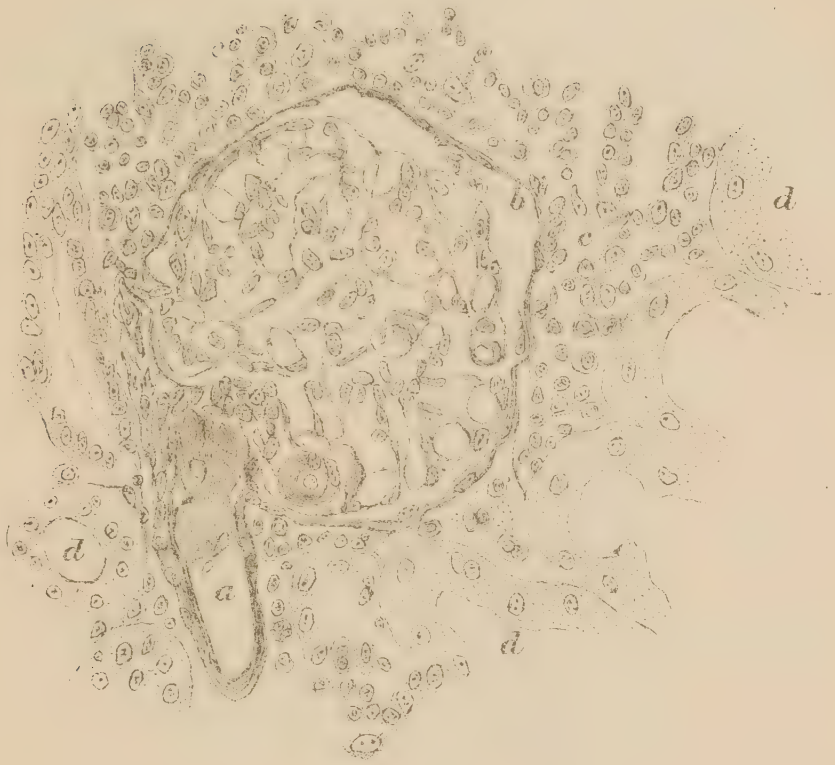

Fig. XV.

Fig. XVI.

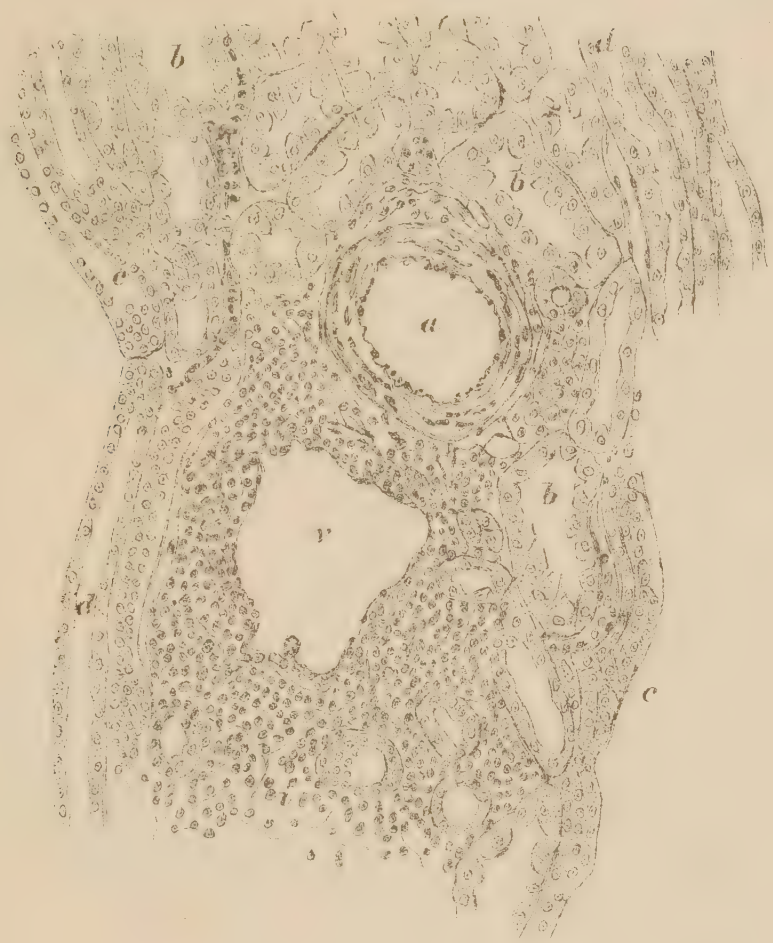

Fig. XVII.

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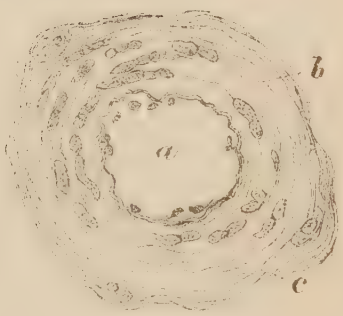

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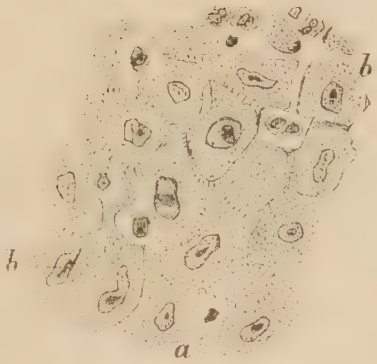
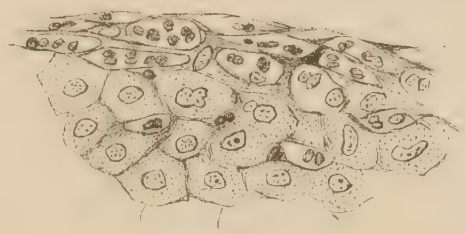


Fig. XX.



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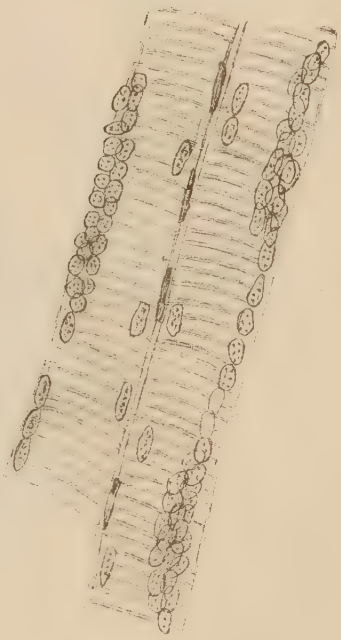

Fig. XXI.

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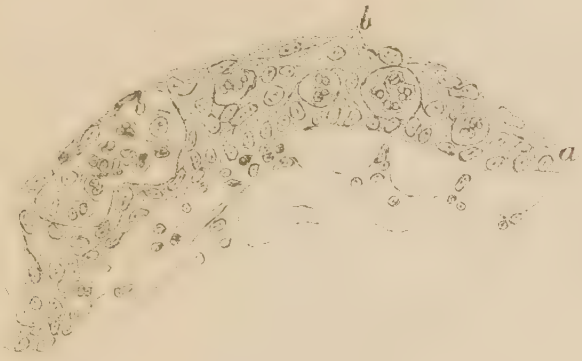

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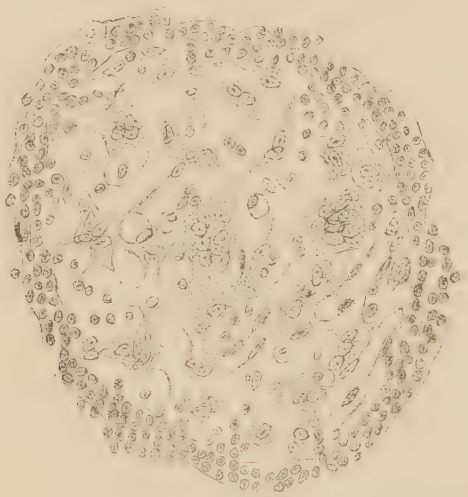

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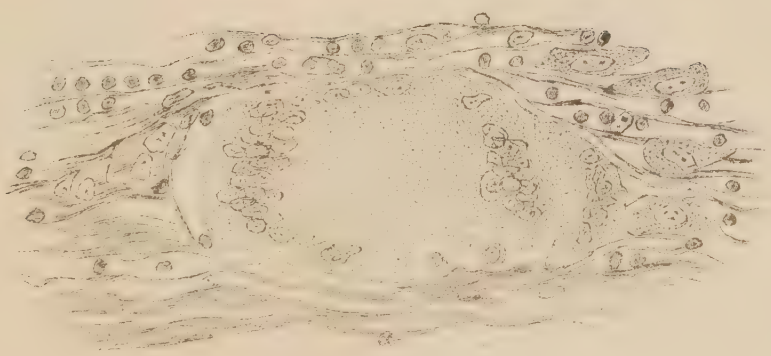

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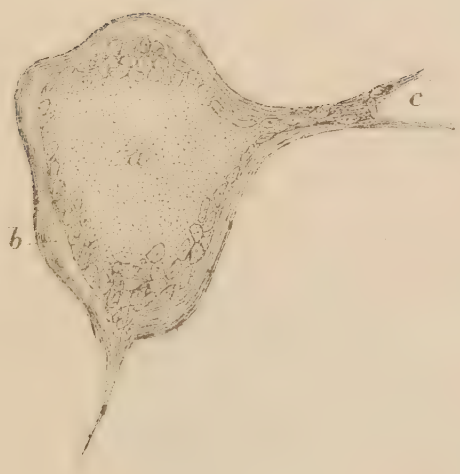


Fig. XXXI.

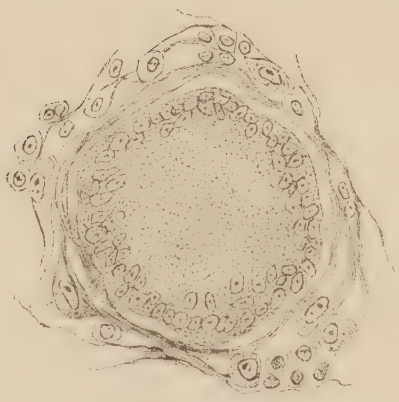
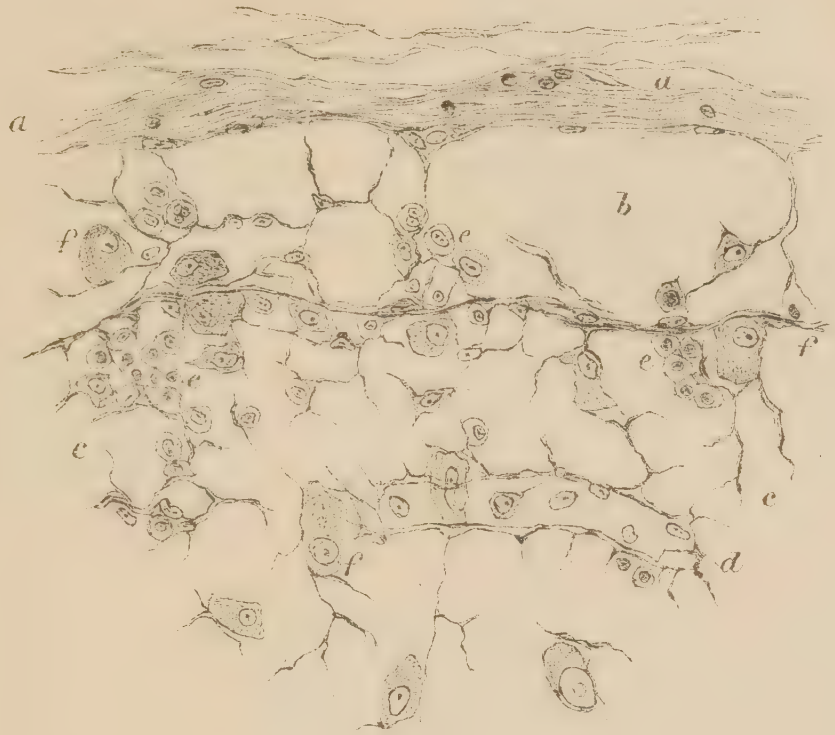


Fig. XXXII.



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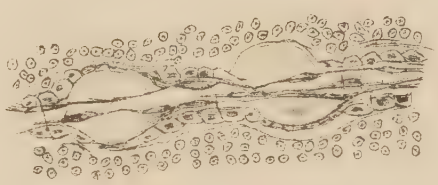

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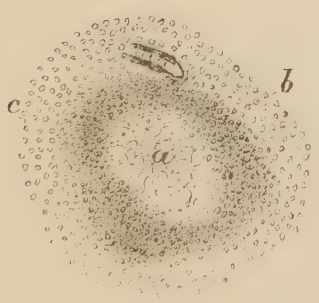

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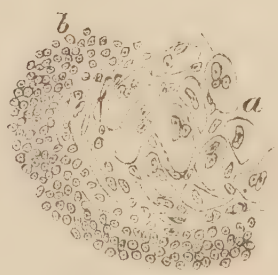

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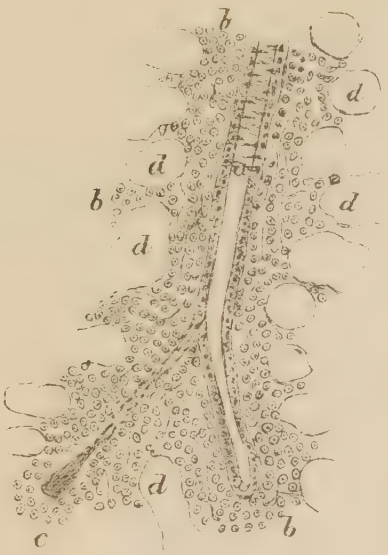

Fig. XXXVIII.

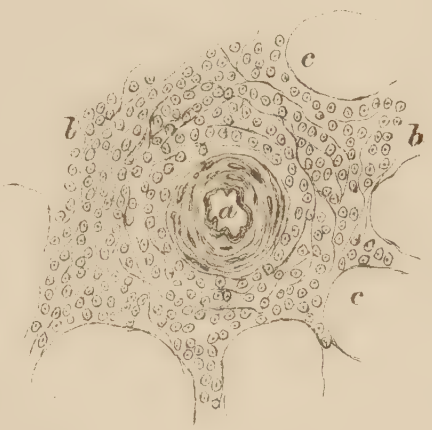

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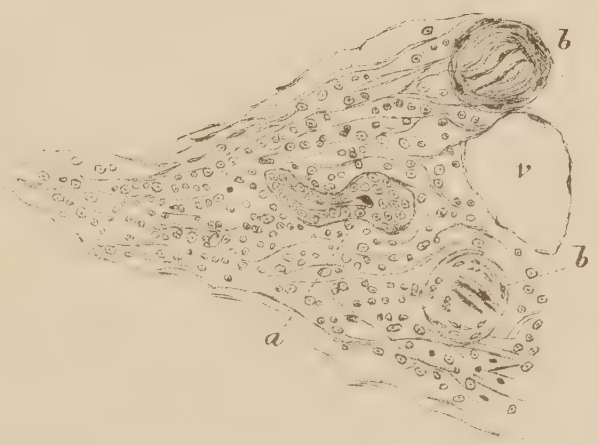
Fig. XL.



No. 4.

Report on the so-called Enteric or Typhoid Fever of the Pig, by Dr. Klein.

I propose to give in this memoir a preliminary account of the results of an inquiry into the disease commonly called Pig-typhoid. Dr. Budd, in a lecture to the Members of the Royal Agricultural Society in 1865, and in his well-known treatise on Typhoid Fever, speaks of this disease in the pig as of the "exact counterpart of typhoid fever in man;" and Professor Wortley Axe, in his recent remarks on typhoid fever in pigs (the "Veterinarian," July 1875, p. 489) concurs with this assertion of Dr. Budd, by trying to show that in etiological, clinical, and anatomical respects both diseases are identical.

Being myself engaged in studying the anatomy of typhoid or enteric fever in man (see No. VI. of this series of Reports, 1875), I was naturally anxious to see whether more light could be thrown on this disease by an experimental and anatomical inquiry into its "counterpart" in the pig. I was therefore greatly disappointed when at the very outset of this inquiry I found that in an anatomical sense the two diseases are essentially different from each other.

It is admitted by all pathologists that the anatomical lesions in human typhoid are of so definite and specific a character that by them, and by them alone, the disease can be recognised in most cases. As I shall show, the anatomical lesions in pig-typhoid are likewise of a very specific nature, being not only very characteristic of this and no other disease in the pig, but also essentially distinct from the human typhoid. It is true the pig-typhoid bears some resemblance to real typhoid in man, but this resemblance is not greater than that amongst infective diseases in general. As is well known, pig-typhoid is a highly infectious disease, associated with an eruption of the skin and ulceration of the large intestine. It has been assumed that the intestinal discharges are the carriers of the contagion, but this assumption seems not to have rested on any direct experimental proof; though from Professor Axe's experiments, it appears that lymph from the pustules of the skin of diseased animals has the power of producing the disease when inoculated into the skin of healthy animals.

I have succeeded in proving, experimentally, that the disease can be produced by inoculating into healthy animals matter obtained from the ulcerations of the intestine; and likewise that the blood of the diseased animals, at a stage when all symptoms are well developed, does not necessarily contain the contagium. In the latter respect the pig-typhoid is essentially different from anthrax, with which it is usually confounded by continental writers on account of a certain similarity of the anatomical appearances in the two diseases; for in anthrax the blood, as is well known, is pre-eminently loaded with the contagium.

A.—The experiments to be recorded in the following have been carried out in conjunction with Mr. W. Duguid, veterinary surgeon at the Brown Institution. They were all performed on young animals.

Experiment 1.—Two perfectly healthy pigs were fed on a piece of large intestine full of ulcers; the material was used perfectly fresh, just as it was removed from the animal that had been killed for the purpose of the research. The animals remained perfectly healthy.

Experiment 2.—Small pieces of the spleen of a typhoid pig, full of whitish nodules of different sizes (*see* the following chapter), were rubbed up with three-quarters per cent. saline solution; of this material one healthy pig received a considerable quantity as food; a few divisions of a Pravaz syringe of the same material were injected into the skin of the groin of another healthy pig. The first animal died on the eighth, the other on the twelfth day; in both cases the "typhoid" symptoms were very well marked.

Experiment 3.—A healthy pig received into the skin of its right groin half a syringe full of the blood and juice of a swollen lymphatic gland, taken from an animal recently dead of the disease, and in which all the anatomical appearances were very well marked. The infected animal showed no signs of the disease for sixteen days, except a small hard nodule (the skin not adherent) in the subcutaneous tissue at the seat of the injection; so that we are quite justified in assuming that the result of the experiment was negative. And this is of very great importance, inasmuch as it tends to furnish direct additional proof of the difference between anthrax and the disease in question; the former being pre-eminently infectious through the blood.

Experiment 4.—From the same pig as in preceding experiment, fresh material was obtained (by scraping) from an ulcer of large intestine, and this material, having been suspended in three-quarters per cent. saline solution, was injected into the skin of the groin of a healthy animal. After ten days, the animal died, with exceedingly well-marked appearances of pig-typhoid in skin, intestine, lung, and lymphatic glands. The inguinal lymphatic glands near the seat of inoculation were especially enlarged, and deep red. The soft palate was swollen and contained follicular ulcerations.

Experiment 5.—Ulcerated parts of intestine of the same animal as that used in experiments 3 and 4 were kept macerating in water for three days, and then swallowed by a healthy animal. This animal died after thirteen days, under very marked symptoms of pig-typhoid: the appearances of skin, intestine, lung, lymphatic glands, &c., being exceedingly well developed, much more than in experiment 4.

The experiment does not, however, prove, as it seems to do, contrary to the experience of experiment 1, that the disease may be communicated by the food; for the very important fact of the infective material having had to be introduced by force must not by any means be lost sight of, as rendering more than possible that in the struggle superficial injuries to the mucous membrane of the mouth may have been the means of effecting inoculation, and that, therefore, this experiment 5 may belong to the same category as experiment 4, *i.e.*, inoculation through direct injection into the connective tissue of the integument. Whether this is so or not we intend to determine by new experiments.

Experiment 6.—The last experiment for the present, but not the least important one, is this: The same animal that had been inoculated with blood and juice of lymphatic glands, and, as we have seen, remained healthy, was again inoculated into the left groin on October 19, but this time not with blood, but with material obtained (by scraping) from an intestinal ulcer of the animal that had died in consequence of experiment 5.

The animal showed very little marked alterations while alive, but, being killed after 12 days, was found to present the following changes: At the seat of the second inoculation there was an abscess in the subcutaneous tissue, this being at the same time closely adherent to the skin. The inguinal glands of the same side much enlarged and very red, so also the lumbar, sternal, and bronchial

lymphatic glands. The two last named had the very characteristic aspect of the lymphatic glands in pig-typhoid : *see* the following chapter. The mucous membrane of the intestine pale, except at the ileo-cœcal valve, which contained a few very small defects of the mucosa ; and microscopic examination proved unmistakably that the mucosa at the ileo-cœcal valve was diseased, only though a mild degree : *see* the last chapter.

The appearance of the lymphatic glands, and the microscopic examination of the intestine (ileo-cœcal valve) in this case, leave no doubt about the animal having been suffering under a very slight degree of pig-typhoid. This experiment contrasts in an important manner with experiment 3 : for both were performed on the same animal ; but in experiment 3, where blood and juice of lymphatic gland had been used as inoculation-material, no disease was produced, whereas in experiment 6, where material of an ulcer had been inoculated, the animal became smitten with pig-typhoid. It might be argued that the condition of the lymphatic glands and intestine as found after the animal was killed may be, perhaps, referred to the first inoculation ; this objection can easily be disposed of, for the microscopic examination proved the changes of the lymphatic glands and intestine to be of recent date ; and besides the characteristic typhoid charges of the inguinal glands near the seat of the second inoculation are quite conclusive.

It is, however, clear to us that in order to arrive at definite conclusions we have to repeat the experiments. As far as they go at present we are inclined to assume—

(1.) That the skin of the diseased animals contains the contagium, as appears from the experiments of Professor Axe.

(2.) That the ulcers of the large intestine, and likewise the diseased spleen, contain the contagium, as appears from my experiments 2, 4, 5, and 6.

(3.) That the contagium is probably not contained in the blood and lymphatic glands at a late stage of the disease, but before this negative conclusion is accepted, additional experiments are particularly requisite.

(4.) That the disease can be produced by inoculation from intestinal ulcers into the skin, as appears from my experiments 4 and 6.

(5.) That whether the same can be achieved by simple feeding with matter of the intestinal ulcers is doubtful, *see* experiments 1 and 5.

Whether the contagium is also contained in the lung, and whether the disease can be produced by inoculating directly into the blood, are questions which cannot be answered without additional experiments.

B. The following are the appearances presented by our animals at the post-mortem examination :—

(*a.*) *Skin.*—In most of the 12 animals that were examined the skin was affected. The skin about the perineum, symphysis, and groins is swollen and of diffuse red colour, so is also the skin of the neck. The ear-lobes much swollen, especially near the tips, and red. The same of the skin of the nose. In two cases there was no distinct rash, and in one case there were in skin of groins, and especially in both ear-lobes, (a few in former, numerous in latter place) smaller or larger necrotic patches of the superficial part of the skin, including epidermis and corium.

(*b.*) *Intestine.*—Small intestine shows, as a rule, hyperæmia, and in some cases ecchymosis in the mucous and submucous tissue, and the serous covering. In some rare cases the same is seen also in the stomach. Large intestine shows always the most characteristic appearances. There are at least smaller or larger, isolated or confluent,

generally roundish, ulcerations at and around ileo-cœcal valve, the rest of the mucous membrane being hyperæmic, even to ecchymosis. In the highest degree the whole large intestine down to the rectum contains ulcers; in the cœcum they are confluent, and measure several inches, extending transversely as well as longitudinally; while the whole remaining mucous membrane of the large intestine is much thickened, and in some parts the submucous tissue contains large accumulations of blood. The ulcers are of various aspects. The following forms may be seen: very minute, well-defined, prominent, yellowish-whitish specks of the size of a millet or hempseed; then somewhat larger, more flattened, prominent, circular or oval yellowish patches (with which in one case the whole mucous membrane of the cœcum seemed quite covered), of the size of a hempseed, up to about $\frac{1}{8}$ of an inch in diameter; next, flat, circular, or slightly oblong patches, situated on the crest of a fold of the mucous membrane, in size from $\frac{1}{8}$ to 1 inch in diameter, generally black or grey (from bile pigment), except a very conspicuous and, I may almost say, characteristic prominent rim which is yellow. The ulcer generally shows a pale, central, or eccentric disc, around which the rest of the ulcer is arranged as concentric rings. Between these flat ulcers with concentric layers and those uniform, yellowish-white, prominent patches and nodules there are all intermediary form; this is easily understood if it is borne in mind that as the latter increase in size the central part is transformed into that black or greyish mass. Besides these there are very often found on the surface of the mucosa minute whitish specks, just perceptible by the unaided eye. In one single instance have I seen ulcerations of the lower part of ileum. This case had exceedingly numerous ulcerations of the large intestine. The two ulcers of the ileum were quite different from the ulcers generally found in the large intestine, for they were oblong, deep pits, surrounded by a thick, prominent wall of swollen mucous membrane, very much the same as ulcers of human typhoid; on the peritoneal surfaces there was an elevation corresponding to them.

The above-described ulceration of the large intestine of the pig cannot in any way be confounded with the characteristic ulcers of human typhoid; the differences are really striking on the most superficial inspection. The only similarity may be said to exist between those early cases of human typhoid which French writers call *la forme bouttoneuse* (where the mucosa of the lower part of ileum and cœcum is studded with small papular structures due to enlargement of solitary lymph-follicles and local accumulations of lymphatic tissue), and the forms of pig-typhoid where the mucosa of the cœcum is covered with slightly elevated papules or patches; but under any circumstance the microscope reveals a marvellous difference in the two diseases, for in the pig-typhoid these patches whether nodules or ulcers, *have absolutely nothing whatever to do with lymphatic follicles*, whereas in human typhoid we find in the first stage round or generally oblong, prominent, papules or patches of swollen lymph-follicles, surrounded by swollen mucous membrane, after which stage the greater part of the swollen lymphatic patches dies and is finally discharged as a slough, leaving behind a pit-like excavation bordered by elevated overhanging mucosa.

Besides the intestine, the following lymphatic glands present very characteristic appearances; the mesenteric glands, especially those of the large intestine; the bronchial glands; the chain of glands along the thoracic (descending) aorta; the sternal glands; and the submaxillary lymphatic glands. The glands are much swollen, slightly firmer than normal or more or less red, in severe cases dark purple or even black and when cut into letting a considerable amount of red fluid ooze out.

At the same time it may be seen that the chief seat of red colourisation is the cortical part of the gland, from which it extends for a greater or smaller distance into the medullary part according to the greater or smaller severity of the change.

In a few cases we observed ulceration also of the organs of the throat. In one case these were symmetrical ulcerations of the mucous membrane of the gums and cheeks, of the front part of the tongue, of the hard and soft palate, and of the epiglottis. The ulcers were of a dark grey colour; and what was most conspicuous about them was their marvellously symmetrical distribution on the two sides of the above organs. In another case we found follicular abscesses in the soft palate; they were very numerous, and the whole organ was much increased in thickness; there was an extensive ulcer in the median line of the epiglottis next the free edge. In a third case we found ulcerations of the gum and cheeks, of the tongue and hard palate; the soft palate contained numerous follicular abscesses; the epiglottis and the mucous membrane at the entrance of the larynx showed hyperæmia and œdema. The epiglottis in addition was possessed with an ulcer. It is noteworthy that these three animals in which we found affections of the throat came all from the same place. In a fourth case, produced by inoculation of matter from intestinal ulcers into the skin, we found follicular abscesses of the soft palate, the organ being much swollen.

The morbid condition of the lymphatic glands is sometimes, to naked-eye inspection, very slight indeed; besides the swelling of the gland there may be only what appears a slight hyperhemic condition; but even here the microscope reveals in all cases a very characteristic state, namely, a bursting of blood vessels in the cortical tissue, and hæmorrhage into the lymphatic follicles and sinuses of that part, amounting in severe cases to total destruction of the adenoid tissue by blood. In severe cases the medullary sinuses, and partly also the medullary lymphatic cylinders become filled with extravasated blood. In so far this condition is similar to what is found in anthrax. Now, this state of the lymphatic glands is, as I said, very characteristic, and, combined with the disease of the intestine, is of paramount importance for the diagnosis.

Further important symptoms, and which have not hitherto received due attention, are affections of the lung and serous membranes. Especially the lung-affection has shown itself to be as constant as any of the preceding, even more constant than that of the skin. The state of the lung is this: the slightest degree consists in a distinct mapping out of the lobes and lobules by œdema of interlobular tissue, the lung-tissue of the corresponding parts being at the same time hyperæmic. Then these parts become hepatised and transformed into a heavy, airless, red, transparent tissue; and subsequently smaller or larger opaque or white specks and patches appear in the red substance, and, as they increase in size, become gradually confluent. On a section it may be seen that this is due to the fact that the bronchial tubes become gradually filled with a white, brittle, cheesy mass, progressing gradually from the finest ramifications on to the larger branches of the affected lobules and lobes. Finally the whole lobule is transformed into a discoloured, dry, hard, friable mass. The pleura of the corresponding parts is of course inflamed, being in some cases exceedingly thick, and covered with false membranes. In severer cases the greater part of one lung and portions of the other may be thus changed, and on the external surface there may exist smaller or greater ulcerations. Except in very light cases there is generally a certain amount of pleural exudation; and in severer cases the pleura contains a considerable quantity of a thick, offensive, yellowish, or discoloured exudation. In some severer cases the pericar-

dium is also inflamed, containing a large quantity of exudation, and its walls being much thickened by false membranes. The same is also the case with the peritoneum, this being in some cases hyperæmic in parts, or even covered with solid lymph and pus. We have had cases where there was no skin eruption, slight intestinal change, and extensive pleuro-pneumonia, pericarditis, and pleuritis.

The next organ of importance is the spleen. The spleen is of dark colour and sometimes enlarged; in some cases it appears not altered in size. In one case it was remarkably enlarged, having throughout it irregular nodular structures, from the size of a pin's head to that of a pea or even larger, whitish in appearance and of firm consistency.

The liver is in severe cases enlarged and very full of blood. The kidney is sometimes also changed: there is hyperæmia of the pyramidal parts, and underneath the capsule, which may be easily stripped off, there are visible on the surface of cortex hæmorrhagic round spots of the size of a pin's head, while similar spots, but scarcer, are met with in the cortex and pyramids. The severer the case the more numerous the hæmorrhagic spots.

Thus we may say that the skin, large intestine, lymphatic glands, and lungs are the organs most commonly affected, and that changes of the serous membranes, the spleen, liver, and kidney, and likewise of the organs of the throat, are of less constant occurrence.

(C.) Microscopic examination.

(1.) *Skin.*—I have examined the microscopic character of those parts of the skin which show the diffuse redness, and in which the skin is being at the same time thicker than in normal parts. The longer the animal lives the more swollen become these parts, as is best shown on the ear-lobes: the pendent parts of these becoming transformed into deep-red, thick, puffy masses, from the surface of which the epidermis peels in greater or smaller flakes. Not seldom are there to be seen smaller or larger roundish or irregular brownish blotches and scabs on the ear-lobes as well as groins and skin of haunch, which blotches and scabs correspond to a necrosis of the corresponding parts of corium. The microscopical characters are these: in the lighter cases as in the earlier stages the corium is œdematous, as is very beautifully shown in the skin of the ear-lobes near the apex by the exceeding distinctness of the lymphatic vessels and the distended interfascicular lymph-spaces which are easily traced to open into the lymphatic vessels. The blood vessels of the corium (including arteries) are more or less distended and filled with blood or plugged with fibrin. Generally the fibrinous plug does not fill up the whole length or breadth of the vessel, nor does it present the ordinary aspect of fibrin in the blood vessels *i.e.*, a felt-work of fibres, but resembles a yellowish cylinder, of so dense a structure that the constituent fibrils are hardly distinguishable; other parts of the vessel contain blood. It is clear from this that there has been existing in the vessels stasis of blood, and that this latter has undergone congulation.

Around the vessels we find lymphoid cells; besides these we find in some cases a very great number of large coarsely-granular cells very deeply staining in hæmatoxylin, with a relatively large, clear, vesicular nucleus; the same cells will be mentioned as occurring in the intestine. The sweat glands are greatly distended, and often filled with blood more or less charged. The connective tissue of the corium contains, in a more advanced stage, in its distended interfascicular lymph-spaces, fibrinous exudations, and in still later cases the tissue becomes more or less flooded with lymph-cells starting from around the vessels and extend-

ing into the interfascicular spaces. And finally the superficial parts of the corium change into a necrotic decolourised mass, the elements of which break down and are transformed into débris. On the ear-lobes, and also in other parts of the skin, I have seen the epidermis becoming very much thickened when the inflammation has reached a high degree.

(2.) *Intestine.*—The mucous membrane of the large intestine shows the following changes. The capillary vessels next the surface very much distended and filled with blood, occasionally ruptured, so that blood is extravasated in the mucosa underneath the epithelium. Generally the epithelium at the mouth of Lieberkühn's crypts detached and in the act of breaking down. The same is the case with the epithelium covering the mucosa around the mouth of the crypts; at these places the epithelium is raised from the mucosa by the presence of cavities filled with fluid, in which are suspended cells, granular matter, and blood. The epithelium of these parts is quite different from the normal condition, the cells being much shorter, and their nuclei swollen up; this leads to the cells breaking up into small elements; and finally the epithelium is altogether discharged. The mucosa is at the same time much thickened by the presence of lymph-corpuscles. The lymph spaces around Lieberkühn's crypts distended. In the superficial parts of the mucosa, as well as in the submucosa, there are in most parts present large uninuclear cells, which are conspicuous by their coarse granulation, and staining very deeply blue in hæmatoxylin. They are present also in great numbers in the connective tissue of the lymphatic glands, and also occasionally in the skin (see above). In the mucosa of the large intestine, and in the lymphatic glands, they are seen to be of the most different shapes: spherical, oval, spindle-shaped, branched, or irregularly drawn out; and this difference in shape makes it very probable that the cells in question are amœboid. The Lieberkühn's crypts are, as a rule, full with mucous secretion; the cells of the epithelium, especially in the outer portion of the crypts, are goblet-cells filled with mucus. In parts more affected the epithelium of crypts is loosened, and at some places perfectly removed from the glands. In other glands the nuclei of the epithelial cells are enormously enlarged, and the cells changed into spindle-shaped or irregular bodies. In this condition we find the mucous membrane over most parts of the large intestine. In some cases there is copious hæmorrhage in the submucosa, or rather the lymphatic vessels of the submucosa are very much distended and filled with blood, derived, no doubt, from broken vessels. In that blood we find, however, hæmatoidin crystals, and besides a peculiar arrangement of the blood corpuscles; these are arranged around spherical larger or smaller masses, which possess a very uniform and finely granular aspect.

The muscular coat of the intestine is also much swollen, varying to œdematous condition. The fat cells of submucous tissue are mostly filled with a mucous matter.

From the above condition of distension of blood vessels, loosening and partial or total removal of epithelium, we have all intermediary forms to the necrosis and disintegration of the most superficial portions of the mucosa, commencing as very small circumscribed opaque spots in which the tissue is disintegrating, and rapidly increasing in breadth and depth. There is no doubt whatever that the "ulcerations" of the large intestine are merely due to a necrosis of the most superficial part of the mucosa. That part in which the necrosis started remains, as has been mentioned, discernible for a long time as a more or less well-defined speck, around which successive new layers of mucosa have more or less concentrically undergone necrosis.

The submucosa shows at the same time, next the muscularis mucose, a reactive inflammation: being full of pus-corpuscles. As the necrosis spreads, the infiltration of the deeper parts with pus-cells increases. Generally the muscularis mucosa seems to be the boundary up to which the necrosis proceeds. In some cases, however, the corresponding part of the submucosa appears likewise involved in the process.

From and even before the first signs of necrosis of the mucosa, viz., when the epithelium begins to break down and be shed from the surface, there are found masses of micrococci, which in some ulcers occupy a great portion of the débris. Also ova of nematode worms I have found in the débris of some of the smaller ulcers.

What we have said hitherto is, I think, quite sufficient to convince anyone that the "ulceration" of the mucosa of large intestine in the pig has absolutely nothing in common with the ulceration of the intestine in typhoid fever of man: the latter being a process entirely limited to the lymphatic follicles of the intestine, which have previously become highly inflamed and hypertrophied.

There are several other points which must be mentioned here, both of great histological interest, and also because of their importance to a right interpretation of the naked-eye appearances of the disease. In some cases when the ulcerations of the intestines are very numerous, the solitary lymph-follicles are seen to be enlarged and peculiarly changed. On the naked-eye inspection we perceive in those cases, in the mucous membrane, translucent spherical nodules, from about the size of a pin's head to hemp seed, or larger, which possess an opaque white centre. Examining them under a microscope we find that in the submucosa there is a larger or smaller saccular cavity, lined by columnar epithelium, and filled with more or less broken-down pus-cells, mucous matter, and granular débris; the wall of the sac containing a few rudiments of Lieberkühn's crypts, is surrounded by adenoid tissue; the cavity of the neck is in communication with the free surface of the intestine by a broad canal occupied by a plug of the same substance as found in the cavity. The plug of the neck and sac generally falls out during preparation. Mr. W. A. Shoolbred, late of St. Bartholomews' Hospital, who examined for me these structures in mucous membrane less changed, found the following: There exist numerous flask-shaped invaginations of the mucosa into the submucous tissue, which flask-shaped cavities are lined by epithelium like the mucosa; the body of the flask situated in the submucosa contains Lieberkühn's crypts like the other parts of the mucosa, with the difference that they are much larger at their blind ends. The flask-shaped invaginations are, as a rule, imbedded in, or surrounded by, a lymph-follicle.

Now it is easy to understand the above condition described as translucent nodules with an opaque centre. One has only to bear in mind: that when the mucosa of the surrounding parts is much inflamed, the cavity and neck of the flask-shaped bodies become filled with pus-cells (gradually breaking down) mucous and granular débris; that under these conditions this cavity becomes more and more distended; and that also the Lieberkühn's follicles in their wall, through stretching, become gradually lost. The tissue of the lymphatic follicle becomes compressed into a narrow zone as the flask-shaped body becomes more distended. Where, however, the flask-shaped bodies do not become plugged up we find this condition: abundant mucous secretion taking place in the Lieberkühn's crypts of the neck, enlargement of the lymphatic follicle around the body of the flask-shaped gland, and penetration of the adenoid tissue into the cavity of the gland, the progressing adenoid issue, however, breaking down when in the cavity of the gland. At

these places the epithelium of the bottom of the Lieberkühn's crypts appears to be changed into a uniformly granular mass with numerous nuclei ; the outlines of the individual epithelial cells having disappeared these masses split into several "giant cells," *i.e.*, huge granular masses, with a great number (5, 20, or more) of small vesicular nuclei ; whether these giant cells originate from the epithelium of the Lieberkühn's follicles in the manner just described or not, it is certain that at these places the lymph-follicle contains them. But also in other parts of the intestine have I seen "giant cells:" that is to say, where the intestinal mucosa has been moderately thickened, and the surface epithelium at some places has become disintegrated, I have observed in the distended lymph-spaces around Lieberkühn's follicles, huge cylindrical or irregular shaped, finely and uniformly granular masses, at one peripheral place of which were embedded very numerous small elliptical or staff-shaped, or spindle-shaped nuclei, deep stained in hæmatoxylin. The corresponding crypts were much changed, the epithelium being transformed into a thin granular layer in which the nuclei might still be seen, and the cavity of the crypts being distended at some places, and containing masses of lymph-cells, which, however, were in the act of disintegration. Generally at the place where the "giant cell" was found the wall of the crypt was seen to be broken, and in communication with the lymph-space around. Similar giant cells I have found in lymph-spaces in the deeper parts of the mucosa, even extending into the submucosa through the muscularis mucosæ ; and finally near the epithelium of the surface where they presented, however, more the round aspect of "giant cells," *i.e.*, their nuclei more like vesicular structures and distributed through the greater part of the centre. I find the giant cells not in all cases, but chiefly in those in which the above-named nodular structures, *i.e.*, swollen flask-shaped glands and enlarged lymph-follicles, are numerous ; and generally they are to be found not far from parts containing the flask-shaped glands and lymph-follicles.

With regard to the ulcerations of the mucous membrane of the mouth, gum, hard palate, and tongue, I have to state that here also the ulceration consists in a necrosis of inflamed mucous membrane, in a breaking down of the superficial parts of the mucosa into a coloured débris.

There is one more point which I believe deserves careful attention. In the ulceration of the tongue just mentioned, and at a time when the superficial scab has not become removed, I have seen masses of micrococci situate chiefly in the tissue of the papillæ, but at some places reaching as far deep as the inflammation extends. That they are micrococci was proved by their forming lumps of uniform granules ; these lumps stain deep purple-blue in hæmatoxylin, and are thus very conspicuous, and besides resist the action of caustic potash, with which all the rest of the tissue disappears. These heaps of micrococci in locality correspond to the papillæ, and are on the surface of the scab, but underneath the covering epithelium, some parts of this having changed into a dry, hard, discoloured mass, others containing larger or smaller vesicles filled with fluid.

In the soft palate we generally find the lymphatic follicles greatly increased, and the mucous glands much inflamed and infiltrated with pus-cells : the number of these latter increasing, the tissue of the mucous glands becomes destroyed, and minute abscesses are formed which discharge their contents through the duct of the mucous gland, which duct has naturally become greatly distended.

(3.) *Lymphatic glands.*—Corresponding to greater or lesser redness of the lymphatic glands we find the cortical parts occupied by greater or

smaller masses of blood, the adenoid tissue becoming at the same time destroyed. But this destruction, of course, depends on the amount of blood present. In the most acute cases we find not only great portions of the cortical follicles transformed into an almost uniform red mass, *i.e.*, swamped with blood, but also some of the medullary cylinders saturated with it. All the lymph-sinuses are in this case also filled with blood, and hence a very striking appearance is produced in some parts: the adenoid cylinders being still intact, while the lymph-sinuses between them and the connective-tissue trabeculæ, are much distended and filled with blood. We may say we have in some parts a very good injection of the lymph-channels with blood. In the cases in which I found (as above mentioned) in the extravasated blood of the sub-mucosa of the intestine the peculiar spherical granular lumps, I met also in the lymph-sinuses of the medulla the same spherical granular lumps. In some mesenteric glands some of the cortical as well as medullary sinuses are filled and distended by fibrin and granular débris, which materials also extend on to the adjacent adenoid tissue. I have seen glands, in which large portions of the adenoid tissue were entirely replaced by fibrin and granular débris..

In the glands from cases of somewhat longer duration, and where there has been extravasation of blood into the cortical adenoid tissue, we find the adenoid tissue in general considerably hypertrophied, and the lymph-sinuses filled with cells of different sizes and aspect. In meselnteric glands of some cases I have found enormous numbers of the giant cells filling up the lymph-sinuses of the medulla. These "giant cells" I can trace down to small granular cells with two or three ellipticai clear nuclei, looking very much like epithelial cells. A very striking appearance is produced in some parts, when the lymph-sinuses of the medulla contain giant cells of various sizes closely arranged one at the side of the other: some of the larger ones, containing 20, 30, and more nuclei, seem to break down at their edges into small granular fragments. The connective tissue trabeculæ contain ordinary lymph-cells, and in some cases a great number of the coarsely granular deeply stained wanderers.

(4.) *Organs of Respiration.*—As has been mentioned, the epiglottis showed ulcerations only in a few cases. I have before me preparations through the epiglottis, the submucosa of the posterior surface being in a state of necrosis, and near the edge so broken down as to leave there a deep ulcer, while the mucous membrane of the anterior surface is only slightly inflamed in its submucous tissue: in this I find lymphatic vessels filled with micrococci, *i.e.*, uniformly granular masses stained conspicuously blue by hæmatoxylin, the "granules" becoming more distinct after treatment with caustic potash.

In addition to what has been said of the changes presented by the lungs, I have to mention that the lung is the seat of lobular pneumonia. The walls of the air-cells thickened by round cells and the cavities of the former containing lymph-cells, changed epithelial cells, and in some instances also smaller or larger "giant cells." In the last stages or higher degrees the inflamed tissue becomes transformed into a necrotic disintegrating mass. In the infiltrated, firm, more or less disintegrating parts I find great masses of micrococci filling up capillaries and veins and also contained in lymphatics around arteries. They may be found also in minor bronchi which have become completely blocked up by cheesy inflammatory products, but there the masses of micrococci, conspicuous by their blue colouration in hæmatoxylin preparations, are generally present in greater or smaller lumps between the outer surface of the plug and the wall of the bronchus. In one case I found ova

of Nematode worms in the tissue of the inflamed parts, and in the larger bronchi bundles of the worms themselves.

The pleura is much swollen, and contains great numbers, continuous layers, of lumps of micrococci. The free surface of the membrane is in many parts covered with them. The exudation fluid is also charged with them, as has been mentioned above. The lymphatic vessels of the surface of the lung (the subpleural vessels) are greatly distended and filled with fibrin ; also the different trunks situated in the septa of lobes.

With regard to other organs, as particularly the liver, spleen, and kidney, my investigations are yet too incomplete for me to make definite statements ; except as regards the liver, that its interlobular connective tissue is greatly altered, by infiltration with lymph-corpuscles, which at some parts form considerable accumulations, amounting almost to nodular new-growths. Similar accumulations of lymph-cells may be observed within the acini of the liver of more advanced cases.

No. 5.

On Infectiveness of Cancerous Tumours, by Dr. Creighton.

Report on the Infectiveness of Cancerous Tumours, with special reference to Infected Lymphatic Glands, by Dr. Creighton.

The following report will contain a summary account of the work done by me from October 1875 to April 1876, when my investigations came to an end. The report will not present conclusions of the same definiteness as my last report, which gave the results of an investigation that extended over a much longer period. But it will be possible to state broadly the questions that have arisen, and to point out where the observations are defective.

The subject of inquiry was the infectiveness of malignant tumours, as manifested in the secondary formations in the viscera, but chiefly in the secondary transformations of lymphatic glands near to or remote from the primary tumour. The primary tumours were of various kinds, including (1) sarcomatous tumours, growing from bone, periosteum, or other connective-tissue parts, both in the human subject and in the dog; (2) tumours of the stomach, which were in two of the cases more lymphomatous than "cancerous;" (3) one case of cancer of the rectum; (4) tumours of the mamma, both in the human subject and in the dog and cat; and (5) miscellaneous cases, including a remarkable case of what seemed to be primary cancerous disease of the liver in a dog, with infection of portal and mesenteric glands.

The lymphatic glands in one part of the body or another were the commonest seat of infection from the primary tumours, whether these were of connective-tissue or epithelial origin; that circumstance is in accordance with the well-known fact that infection is often found to have reached the lymphatic glands, but to have stopped short of viscera such as the liver and lung. The liver and lung were the seat of secondary tumours in a large proportion of the cases, sometimes the one organ being affected and sometimes the other, and not unfrequently both. Two highly instructive cases occurred, in which both ovaries were secondarily infected, but time did not permit of that valuable material being made the most of. The infected lymphatic glands of which preparations were made, were derived from upwards of twenty different cases. There were, besides, several cases with secondary tumours in the lung or liver, but without any obvious affection of the lymphatic glands.

The one generalisation that stands out conspicuously from the examination of the whole collection of cases, is that the secondary tumours correspond in structure to the primary, even in the most minute particulars. There are, no doubt, some apparent exceptions to the rule; but in the great majority of cases the resemblance is at once apparent, and it is a resemblance of so surprising a degree, that there is no mistaking the significance of it.

The well-established fact of a minute resemblance between the primary tumour and its secondary or infective products affords an invaluable clue to the nature of the infective process as regards tumours. By establishing, at the outset, that resemblance or family likeness between a primary tumour and its secondary products, we are led to conclude that the infectiveness of primary tumours is a property that they develope of themselves, and that no extraneous agency plays any conceivable part therein. In my last report on the physiological processes of the mammary gland, and on its pathological processes as

related to the physiological, I showed that tumours of the breast were attributable to certain departures from the physiological regularity of the gland, and that they were, in fact, the consequences of functional disturbance and the expressions of the same. As that is an entirely novel and apparently *outré* conception of tumours, I think it necessary to say that my former report contained a full statement of details, and that it represented investigations carried on for a considerable period. Taking, then, the conclusions of that report as a basis, and selecting, for the purpose of illustrating the present subject, a case of mammary tumour with secondary tumours or products of infection, the following points as regards the infection become clear.

The primary tumour is the mammary gland, or a portion of the gland, more or less modified in its structure through aberrations of its function. The functional disturbances are never exactly the same in any two cases, and the respective modifications of structure, or, in other words, the structures of the respective tumours, are never exactly the same. Although there are necessarily more points of likeness than of unlikeness in two cases of tumours of the same organ, arising at corresponding periods of life, or under corresponding circumstances generally, yet each tumour has its distinct individuality. There are the same differences among individual tumours as there are among individual persons. Now, it is the individuality of the tumour that is reproduced in the secondary tumour. That fact is so remarkable that the attention s at once arrested by it, and it is no less striking as a phenomenon than significant as a point of argument. If the secondary tumour reflects the individuality of the primary, it is obvious that the infective influence emanates from the primary tumour, and that it is a property of the latter developed within it, and seemingly independent of all extraneous influences. Whatever the nature of the infection may be, it appears certain that it is derived in the most intimate way from the primarily diseased part. In other words, the infectiveness of a tumour is a property of the cellular elements of the tumour and of their juices.

The investigation was then directed to find out more particularly the nature of this infective property, and the mode of conveyance of the infection to the neighbouring lymphatic glands and to the viscera. In my first report I arrived at the conclusion that secondary nodules in the liver sprang up throughout the organ, through a process of endogenous cell-formation that took place in the liver cells at particular spots. The new cells, formed more or less obviously out of the liver cells after the endogenous mode, became the secondary tumour cells. The examination of other cases of secondary liver tumours, collected in the interval, confirms this view. The process was especially well marked in cases of lymphomatous tumours. The secondary tumours of the lung are a more difficult subject ; but it may be mentioned that the endogenous process of cell-formation is found to be in progress in an unusually clear way in lung alveoli forming the boundary or the periphery of tumour nodules, the greatly swollen epithelium of the alveoli being the cells in which the endogenous process was taking place. The two cases of secondary ovarian tumours, so far as they have been investigated, appeared to be highly instructive as regards the nature of tumour infection. The ovary appears to be the only part liable to secondary tumour process which impresses a certain character of its own on the secondary growth, or remains other than passive under the working of the infection on its tissue-elements. In each of the two cases of tumour infection, both ovaries were affected and both were *cystic*. One of the cases occurred in Mr. Simon's practice, at St. Thomas's Hospital, in a girl aged 18, who had a sarcomatous tumour growing from periosteum at the

metatarsus, with infection of the inguinal lymphatic glands on the same side, as well as of other lymphatic glands within the abdomen, and with secondary tumours of the lungs. The tumour process could be seen in the stroma of the ovary in various stages, and at some points the exact periosteal overgrowth of the primary tumour was reproduced. The other case occurred in a bitch, that had suffered from mammary tumours for several years. The "sympathetic" connexion between the ovary and mamma may serve to exclude this case from the category of pure infections, and the case is otherwise too difficult to be gone into here without further study of it. It was specially to the infective process in lymphatic glands that attention was directed in the present inquiry; and the rest of the report will be occupied with an account of my somewhat inconclusive examination of infected lymphatic glands, with particular reference to the nature of the infection derived from the primary tumour, and to the form in which it was conveyed.

This subject has not hitherto engaged a great deal of attention, but there have been several important contributions to our knowledge of it within the last twenty years. In particular, Professor Billroth has made investigations of the lymphatic glands in a variety of infective processes, including, among others, those of acute inflammation, scrophulosis, typhoid fever, and cancer.* The infected mesenteric glands in typhoid fever were studied by Virchow, and compared with the lymphatic glands in other infective processes.† The infection of axillary lymphatic glands in a case of cancer of the breast has been described by W. Müller.‡ The general question of lymphatic gland infection has also been treated of by Hansen,§ with special reference to leprosy and scrofula. A more than usually elaborate account of the infection of bronchial glands in a case of cancer of the œsophagus has been published by Gussenbauer.‖ It will not be necessary, in the sequel, to refer to more than the general conclusions of those writers.

Several of the cases in my collection of lymphatic gland infection from tumours appeared to be especially well adapted to show the nature of the infective communication between the seat of primary disease and the lymphatic gland. These were cases of mammary tumours in the bitch, where the lymphatic glands, especially those beneath the inguinal portion of the mamma, were affected with the disease. In the third section of the physiological part of my previous report I described at length the nature of the physiological relation between the secreting gland and its lymphatic glands. The lymphatic gland was a kind of depuratory apparatus, receiving the cellular waste of the secreting gland, and reducing it to the uniform condition of lymphoid cells. The most noticeable and unmistakeable form of waste cells were large nucleated granular cells, containing a yellow or brown pigment. Those cells, being waste products of the imperfect secretion, were conveyed to the neighbouring lymphatic glands in large numbers, and in many preparations they could be seen occupying the lymph sinuses. The pigmentation of the cells enabled them to be traced easily from their origin within the acini to their final disposal and utilisation in the lymphatic gland. Such, then, being the well-marked relation between the secreting gland and its lymphatic appendage in health, the question naturally arises

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* *Beiträge zur Pathologischen Histologie.* Berlin, 1858; and in *Virchow's Archiv*, Vol. 21.

† *Würzburger Verhandl.* I. 86.

‡ *Henle und Pfeufer's Zeitschrift*, 1863.

§ In a memoir published at Christiania, 1871.

‖ *Archiv für Klinische Chirurgie*, 1872.

whether the "infection" of the lymphatic gland from a diseased mamma is in any way dependent on a modification of the health relationship. If that should prove to be so, the infection of the lymphatic gland would be placed on a different footing from the infection of the liver and lung. The last-named viscera are nothing more than a convenient soil for the infective process to plant itself upon, whereas the lymphatic glands near the mamma are not merely dense masses of parenchyma liable to be attacked by the infection, but they are also physiological adjuncts of the primarily diseased organs, and part and parcel of the secretory apparatus. It will therefore be a first subject of inquiry, whether the infection of the mammary lymphatic glands is in any way incidental to the physiological part that they play towards the secreting gland.

One case may be taken as an illustration of the problem here presented. The tumour occurred in a bitch at the inguinal end of the mamma on one side. It consisted mainly of a thickening of a small part of the mamma and of one or two circumscribed small nodules. In removing the affected part of the mamma, it was found that a cluster of lymphatic glands, lying immediately beneath the mamma and embedded in fat, were both enlarged and otherwise changed, and they were removed adhering to the mamma along with some of their surrounding fat. Two of them were about half an inch long and somewhat less in their shorter axis. On cutting them open there were differences at once apparent in different parts of their substance, certain tracts being deeply pigmented and denser, while other parts were free from pigment and more elastic. The microscopic examination showed in various places a definite new formation. The new structure generally existed within the limits of a follicle. There were two varieties of it. One of them was a structure composed of large rounded spaces lined with a kind of cubical epithelium with large nuclei. This structure closely resembled the appearances in certain parts of the primary new growth. The new structure in another of the lymphatic glands was different. It consisted of long columns of epithelial-like cells extending into the central clear space of the follicles with their extremities free, or forming a network of trabeculæ crossing the area of the follicle. That kind of structure is quite definite and is often found in mammary tumours of the bitch; in this case the primary tumour or the diseased portion of mamma did not show precisely those appearances at any part of it that was examined, but it showed a papilliary kind of structure that had doubtless grown out of an earlier form such as that found in the lymphatic gland.

Leaving as it stands the question of resemblance between the primary structure and that in the lymphatic glands, we shall turn to consider how the new structure in the lymphatic glands was acquired.

The glands, it has been said, were obviously pigmented more at some parts than at others. In the normal condition the same lymphatic glands are often found to have their lymph sinuses occupied by round granular pigmented cells, and the follicles are sometimes found to be strewn with the grains of free pigment. In this pathological case, the most noticeable point of difference is that the large round pigmented cells have overflowed from the lymph sinus into the substance of the follicle. But there are certain other changes in the diseased gland which may or may not be antecedent to, or the cause of the overflow of mammary cells from the lymph sinuses into the follicles. The lymph sinuses themselves are often seen to be more obstructed by their contents than normally. The fibres stretching across them and forming their filtering or depuratory apparatus are broader and thicker, and the pigmented cells that ordinarily pass through them, and become stripped

of their pigment and cell substance in so doing, appear to have taken up as if permanent positions; the lymph passage is in fact clogged up. There is, however, a more general change in the parenchyma of the gland, of which the change in the lymph sinuses is perhaps only a part. Throughout the whole of the gland the lymphoid cells have become swollen. In ordinary circumstances and under ordinary methods of preparation, the lymphoid cells appear as naked nuclei. In the beginning of the infective cancerous process they are all found to have a distinct investment of protoplasm; the nucleus is now surrounded by a margin of cell substance, and the closely-packed cells of the follicles have often a rectangular or polyhedric shape, resembling epithelium. The swelling of the parenchyma is quite general throughout the gland, and it is difficult to say, by what agency issuing from the seat of primary disease, it has been brought about. The swelling of the parenchyma of the secondarily infected organ appears to be the first step in the process of cancerous infection, and the cause of it remains obscure; so that at the outset of the inquiry we have to leave an important point unexplained.

The swelling of the lymphatic parenchyma is not peculiar to the infective process of malignant tumours. It occurs, generally speaking, in every infective process, including acute and subacute inflammation, scrophula, tuberculosis, syphilis, typhoid fever, &c. The resemblance in their initial stage between certain of those processes was made out by Virchow, and between others by Billroth; so that it may be said to amount to a generalisation. In the cases of infected mammary lymphatic glands, it is difficult to decide whether the swelling of the lymphoid cells of the parenchyma preceded or followed the overflow of cells from the diseased part into the follicle, and it remains therefore doubtful whether those cells, by their contact or otherwise, were the agents of infection. But whatever the cells brought from the diseased mamma may have had to do with the initial swelling of the parenchyma, which is common to this particular infective process and to every other infective process, there is little doubt that those cells sometimes determine the permanent structural changes in the cancerously-affected lymphatic gland.

To return to the case of lymphatic gland beneath the diseased mamma of the bitch. The new growth in the lymphatic gland consisted, in some places, of papilliform processes or trabeculæ of epithelial-like cells, resembling a structure of common occurrence in primary mammary tumours. In the primary disease that structure is dependent on outgrowths of the epithelium lining the acini; several varieties of this primary process in the mamma were described and figured in my last report. In the secondarily affected lymphatic gland, the same papilliform processes and trabeculæ occur, and they appear to arise from the wall of acinus-like cavities, just as they did in the acinous gland. How then does the lymphatic gland assume this wonderful imitation of the pathological process in the secreting gland?

In the first place it is the dense parenchyma of the follicles and cylinders that is the seat of the changes; the lymph sinuses may be disregarded for the present. The lymphoid cells of the follicles, it has already been pointed out, have acquired an investment of protaplasm or a fringe of cell-substance round the nucleus. As in the first stage of all the infective processes, the lymphoid cells have acquired something of an epithelial character. In the other infective processes, the swelling of the parenchyma is only a passing phase; the swollen cells undergo rapid changes either in the way of suppuration or necrosis, and the process, if it runs its course, ends in cicatrization. The tumour process is eventually distinguished from all of these; although in some

of the cases of tumours to be afterwards mentioned, there is a resemblance with other infective process beyond the point of parenchymatous swelling. In the particular case, however, that has been selected for the general description, the lymphoid cells permanently retain their protoplasmic investment and become endowed from that time forward with the persistent vitality and power of increase which distinguishes tumour cells.

Up to this point we have found that the cells of the whole follicle become uniformly changed into epithelial-like cells. It is out of that matrix-tissue that a particular structure is carved, according to the pattern of the primary tumour. The compact follicle becomes changed into an acinus-like cavity, with papillary processes rising from its margin (or its floor), and projecting free into its space, or with trabecular bands crossing it in certain regular directions. The carving out of the tumour pattern from the compact cells of the follicle is effected by means of the large granular pigmented cells. These, it has been mentioned, overflow from the lymph sinuses into the follicles. They are frequently seen lying among the cells of the follicles, and in favourable specimens, their agency in transforming the follicle into a portion of new growth after the primary pattern, can be inferred in a general way. Many of them become distended, a cavity forming in their substance; they are thus transformed into large vesicles, which press the follicular cells in certain directions. The vesicles then break down, and the follicular cells remain as epithelial-like processes or trabeculæ, with spaces between them, and looking as if they had grown up from the rows of cells lining the wall of a cavity. In the primary tumour the round spaces, with numerous knob-like or papillary projections, are actual acini of the gland, the lining epithelium of which has taken on the common form of papillary overgrowth. Exactly the same appearance is produced as a secondary result in the adjacent lymphatic gland; and the striking resemblance, or rather the exact copy, is effected by carving the pattern out of the compact mass of cells of the follicle. The carving-out process is accomplished by means of a particular class of cells, which are themselves destroyed in the process. Now the large pigmented cells, through whose agency the pattern of the primary tumour is imprinted on the secondarily-affected lymphatic gland, are derived from the primary tumour, or, in other words, are products of the primarily-diseased gland.

That is, however, only one of the ways in which the lymphatic gland is transformed into the likeness of the primary tumour. Another mode, which is an interesting modification of the first, is as follows. It has been observed especially well in the affected lymphatic glands of a case of mammary tumour of the human subject. The primary tumour in this case is figured on page 185 and again on page 186 of my last report. It is essentially of the same trabecular structure as the mammary tumour of the bitch just described; the enlarged acini are traversed by anastomosing columns of cells. The structure of the axillary lymphatic gland is of exactly the same kind; there is observed in the primary tumour at certain places a quantity of free brown pigment granules, and collections of red blood corpuscles, and even in those small and, as it were, accidental circumstances, the lymphatic gland resembles the growth in the mamma. The development of the new growth can be traced through various stages. The first stage is that of general swelling of the parenchyma, depending not so much in this case on a distinct fringe of protoplasm round the previously naked nuclear lymphoid cell as upon a uniform enlargement of the lymphoid cell in its nuclear state, the cell becoming at the same time more granular. The next stage resembles

that found in the other infective processes. The swollen parenchyma appears to undergo a general atrophy or necrosis. The swollen cells assume an opaque appearance, and fail to colour with the logwood staining fluid. In the other infective processes that stage goes on to the general breaking down of the parenchyma, but in the tumour process the sequel is different. Along certain regular lines throughout the follicle the opaque and, as it were, necrotic cells show a small and brightly-coloured nucleus in their centre. These nuclei are in many cases quite minute points, and such is no doubt their first appearance as young cells in the substance of the old follicular cells. They appear, as has been said, along certain regular lines; and growing up from the old cells along the lines that are as if laid down or marked out for them, they result in a new growth of a definite pattern, the pattern being the structure of the primary tumour. There is in this case, as in the former case, a carving out of the new growth from the compact cells of the swollen follicle, but the carving out is here effected by a residual process. The old cells of the follicle decay except along the lines of the new pattern; and along those lines young cells spring from the substance of the old follicular cells, and in course of time grow up into the form and arrangement of the cells in the primary structure.

A third variety of the mode of transformation of the lymphatic gland substance is found in the epigastric glands in a case of cancer of the stomach. In the primary tumour the epithelial-like cells were collected in alveolar groups between the mucosa and the serosa. The cells lay in the alveolar spaces, packed together without any very definite arrangement. The appearance of the primary structure is simulated in the lymphatic gland in the following way. There is first of all the swelling of the parenchyma; the swollen lymphoid cells then become opaque; and ultimately there arise from them, not along particular lines, but over continuous areas, small young cells, which form the alveolar groups corresponding to those of the primary tumour. But the special interest of this case is in showing the exact mode of origin of the young cells from the opaque and decaying cells of the follicles. The mode of origin is here clearly seen to be that of endogenous cell formation. The young cell lies in a cavity of the parent cell; the smallest of them are minute points like a small nucleus, but even at that stage they seem to lie free in a cavity or vacuole. All the lymphoid cells of the follicle appear to undergo this transformation, and the pale outlines of the old cells can always be seen lying among the endogenous brood even when the latter have reached a considerable size and become independent. I have already described this variety of endogenous cell formation in my first report, treating of the development of secondary tumours in the liver. In the present case of cancer of the stomach, there were affected lymphatic glands of various sizes. It is in the smaller glands that the histogenesis of the new growth can be traced; in a large pigmented gland, the size of a pigeon's egg, the tumour structure is perfect and finished, and the cells have everywhere their epithelial form and arrangement.

The three cases hitherto mentioned are cases where the semblance of the primary tumour was produced in the lymphatic gland by a process of adaptation or carving out of the lymphoid parenchyma. I shall add a fourth case to illustrate the extreme form of this mode of infection. It is a case of a sarcomatous tumour, in the dog, the size of a child's head and growing from the ventral surface of the scapula. The brachial plexus of nerves was carried inwards by it, and spread out over its axillary surface, where the nerves, widely separated from each other, appeared to bind it down like the cording of a bale. The axillary

lymphatic glands were embedded in the substance of the tumour at its axillary periphery. They could be shelled out from the tumour proper, and were also distinguishable by their colour and density. There were at least half a dozen of these embedded lymphatic glands, and they were upwards of half an inch in their longest axis. On examining them, they were found to be uniformly affected, and to be changed throughout into the likeness of the sarcoma which had enclosed them. In some the process of transformation could be traced; in others the process was complete, the individual cells having lost everywhere their lymphoid character, and assumed the size and form of the tumour cells. So far as the preparations went, the process seemed to have befallen the lymphatic glands uniformly throughout their substance. The lymphatic glands were, for the infective process, nothing else than compact cellular masses presenting at all points an equally favourable soil for the infection. The case may be taken as an example of those in which the physiological arrangements of the gland, the relation of the lymph sinuses to the follicles and the like, go for nothing. The lymphatic gland falls a prey to the infective process as if it had been a crude mass of cells, and as if its complex structure and its perfect mechanism were non-existent.

In such cases it appears hopeless to trace the path of the infection, or to inquire whether it came to the lymphatic gland in the form of a fluid, or in the form of cells, or, as some have supposed, in the form of a contagion of organisms foreign to the body. But if the mode of infection in the last of the four cases, and in other cases, chiefly sarcomatous, that might have been given, seems to baffle all analysis and to be referable only to an inscrutable agency, it borders on modes of infection in other glands that are less and less mysterious. The four cases given as examples all show that the infection acted upon the predominant cells of the gland, or upon the lymphatic parenchyma; and in the first of the cases, the co-operation in the infective process of cells derived from the primarily diseased part, or the primary tumour, was undoubted. It is this co-operating or determining agency that has to be further inquired into.

In the first of the four cases, the cells derived from the primarily diseased part were large granular pigmented cells. Those cells are normal products of the mammary secretion at its periodically enfeebled periods, and in the tumour processes of the bitch, they are produced in unusual quantity and at unusual times. They often contribute largely to the bulk of tumours, being collected in large heaps outside the secreting acini, and when they are stripped of their pigmented cell-substance their nuclei subdivide and multiply in the usual way.

In the healthy condition of the mammary function, they are conveyed to the neighbouring lymphatic glands, in whose lymph-sinuses they are reduced to a nuclear or lymphoid condition, and are so utilised as lymph corpuscles.* Now, in the pathological states of the mammary function, as they may be studied in the bitch, the lymphatic glands may continue to perform this task for the waste products of the secreting gland for a considerable time after the pathological process in the mamma is firmly rooted. In the present collection of mammary tumour cases are several in which the lymphatic glands of the mamma, both at the inguinal and axillary ends of the gland, show the normal relations of all their parts; the follicles containing the ordinary lymphoid cells, and the sinuses being filled with the round yellow mammary cells. But

* *See* Section III. of the first part (physiological) of my last report.

it appears that a time comes when the depuratory apparatus of the lymphatic gland breaks down.

There is, first, stagnation of the large granular cells in the lymph-sinuses, and that is followed by an overflow of them into the substance of the follicles. This overflow may be observed in many cases, and there is no doubt of its close connexion with the process of infection. Side by side with the overflow, there is observed a change in the constant elements of the lymphatic gland. That change is the parenchymatous swelling before mentioned, and it is difficult to say whether the parenchymatous swelling of the constant elements of the gland is the cause or the effect of the overflow of waste cells that are in process of passing through it. The swelling affects not only the lymphoid cells of the follicular tissue, but much more the "fibres" of the lymph sinus. Those fibres are protoplasmic bands, and the nuclei that they appear to contain are merely the circulating cells of the lymph sinus in more or less close apposition to them. At the same time that the lymphoid cells of the follicular tissue become individually larger or more invested with cell-substance, the "fibres" swell up into broad bands, diminishing the meshes between them. The lymph sinus thus appears as if it were clogged, and the depuratory process by which the waste cells are reduced to a nuclear state appears as if arrested. It is then that the waste cells from the mamma overflow into the follicles. The real difference between this pathological process and the normal process is that in the latter the waste cells of the secretion are received into the follicle only after they have undergone the depuratory and reducing process of the lymph sinuses, while in the pathological case they enter the parenchyma of the gland in the form of waste cells and with all the properties of waste cells clinging to them, whatever those properties may be. Having reached the follicles in the condition in which they left the mamma, they there play a distinct part in producing the semblance of the primary tumour in the lymphatic gland.

In the first case mentioned the foreign cells determined the pattern of the new growth, or aided in the carving-out of that pattern, while they themselves did not go to make up its bulk. But there is reason to think, from a number of other cases, that the waste cells from the primarily affected part may themselves contribute by their own substance to the production of the pathological structure in the lymphatic gland.

The two modes of infection have been discussed by previous writers, and have been broadly contrasted, and treated as supporting rival theories. Either the lymphatic gland is transformed throughout its whole substance into the likeness of the primary tumour, or certain fragments from the primary tumour are carried into the lympatic gland where they find a lodgment and grow up into a tumour mass, gradually encroaching upon and causing the atrophy or disappearance of the lymphatic tissue proper. The four cases already given as example, are all illustrative of the first theory; but other cases might be given that would appear to support the second.

The same apparent discrepancy or want of agreement occurs throughout the entire literature of this subject, and not only as between different observers, but as between the different observations of the same observer. Thus Professor Billroth in his earliest papers on this subject wrote:—"Regarding the extension of cancers by the lymph-stream, I "cannot entirely share the opinion of those who here assume a direct "transport of cancer-cells, which are merely conveyed to another place, "there to fulfil their destiny. This view is to me somewhat incompre-"hensible, I might almost say it is conceived too much in the sense of "plant-life. In the widest estimate that I can form of the vital

"powers of cells, I cannot imagine that they swim in the lymph-"stream, like fish in the water, or that, like wandering pores, they "require only to fix themselves in order to grow up into new indi-"viduals. It is much more conceivable that the serum (intercellular "substance), conveyed from the cancer has a certain infectiveness for "other cells, and that thereby a new diseased process arises in a "neighbouring part."* Three years later, Professor Billroth returned to the subject, the lymph-stream within the lymphatic gland having been demonstrated in the interval by His and Frey; and in a case of pigmented cancer of the breast, Professor Billroth did find melanotic cells in the lymph-sinuses of the axillary lymphatic glands, and was disposed to conclude that these were the starting point of the secondary new growth. He especially remarks upon the value of pigmented cells in tracking the infective process. "By making out," he says, "that "the cancer-formation in the lymphatic glands follows the lymph sinus, "that is to say, the normal lymph stream, we are again brought face "to face with the notion of a transporting of cancer cells. It appears "so extremely plausible, from this discovery, to think that the cells from "the cancer reach the lymphatic glands by the lymphatic vessels, and "that they there fix themselves and establish a new centre (*Heerd*). "But proof is wanting that cells of this kind can be transported, or "that they are actually found in the afferent lymphatic vessels of the "gland."†

In the present collection of cases are several in which the new growth begins in the lymph-sinuses. Thus in a lymphatic gland beneath a mammary tumour in the cat, the new structure is found at only a few points in the cortical lymph-sinuses; at those points the fibres of the reticulum appeared to constitute the framework of the new growth. In a lumbar lymphatic gland infected from cancer of the rectum, many cells, that can be traced into their ultimate form of tumour cells, lie in the lymph-sinuses, and where collections of them occur in the follicular tissue, those collections are always definitely circumscribed. Again, in the case of lymphatic glands infected from one of the cases of cancer of the stomach, there can be seen in different preparations, various degrees of encroachment of the tumour cells from the lymph sinuses upon the follicles. But many of the lymphoid cells of the follicles retain their lymphoid character to the last, and narrow tracts of them can here and there be seen extending through a gland that is otherwise completely changed into the likeness of the new growth.

In a large collection of infected lymphatic glands from various kinds of tumours, there is no doubt a considerable want of uniformity in the process of infection. But it may well be doubted whether the appearances can be placed in two distinct categories, or be taken to establish two distinct processes. There is certainly no reason to think that one or other of the sets of observations is wrong, and that the discrepancy arises from defective observation. The discrepancies between the accounts of different observers and between the different accounts of the same observer, depend, without doubt, upon differences in nature really existing. The inference from them, at the utmost, would be that there is more than one mode of infection. But a closer examination seems to show that the process of infection in lymphatic glands is in all cases one and the same. The differences depend upon differences in the degree of intensity of the infection. Those differences in intensity are often exemplified in the same case. It is not uncommon to meet with several

* *Beiträge zur pathologishen Histologie*, p. 201–202.

† *Virch. Arch.*, Vol. 21. p. 441–42.

lymphatic glands affected, and these of various sizes, say from the size of a pea to that of a pigeon's egg. It is true that the smaller glands contain more traces of the normal structure than the large, and from that circumstance it might appear as if the larger glands, as found, had been the first attacked, and that in them the new growth had spread farthest. But the most usual difference between the larger and smaller glands appears to be that the larger had from the beginning undergone a more extensive or a more general initial swelling of their parenchyma, whereas the smaller are only affected at limited spots. And those differences may be said to depend on the initial intensity of the infection.

It is by keeping in view this circumstance that the apparently irreconcileable varieties of the infective proces can be shown to be one and the same. There is not one class of cases in which there is a general transformation of the lymphatic tissue into tumour tissue, and another class of cases in which the tumour tissue of the lymphatic gland is derived from the multiplication of primary tumour cells conveyed thither. But there are extreme cases in which the whole parenchyma of the gland appears to be infected at once by some infective agency which cannot be traced ; there are less extreme cases where the whole follicular tissue is transformed by means of cells overflowing into the parenchyma from the lymph-sinuses ; and there are cases of feebler infection where the lymph-sinuses are the starting point, and where the transformation proceeds from them throughout the follicle as if in successive zones or from successive centres. The last-mentioned cases are those in which the new growth has seemed to depend on a multiplication of the transported primary cells, and a gradual encroachment upon and supplanting of the normal lymphatic tissue by them. There is no doubt an encroachment ; but it is not a supplanting and displacing encroachment, but a transforming encroachment.

It will now be necessary to give some of the detailed observations on which the above conclusion is based. In the first of the group of four cases, it was stated that the new growth was carved out of the swollen parenchyma or folicular tissue by the agency of large granular pigmented cells that had overflowed from the lymph sinuses. More particularly, it was by the vacuolation of those foreign cells that the lymphatic parenchyma was adapted, or transformed into the pattern of the new growth. It is to be observed here that there was no vacuolation of the individual cells of the lymphatic parenchyma. The vacuolation or endogenous cell-formation process has been shown in my first report to be the mode of transformation of the liver parenchyma in secondary tumours, and the same vacuolation of the individual cells of the lymphatic parenchyma is now to be described for certain of the lymphatic glands. In the first case, there was a process of vacuolation, but it took place in the foreign or transported cells ; and as the proper cells of the parenchyma were not transformed by that process, those foreign cells overflowing into the parenchyma* may be held to have undergone the vacuolation process *vicariously* for the cells of the part.

The vacuolation process, as an element of the process of tumour infection, can be nowhere seen more perfectly or more unambiguously than in certain cases of infected lymphatic glands. Vacuolated cells are found in lymph sinuses, while the follicles are still in their lymphoid condition. Again, the large protoplasmic cells in which the vacuolation

* This expression is purely figurative, and is used here in the absence of a more scientific explanation of the process, such as a more prolonged study of it will doubtless bring to light.

process takes place are found to have overflowed into the follicles. Sometimes the vacuolating cells form an outer zone to the follicle, at other times they form definite groups in the follicular substance. The products of the vacuolation are the tumour elements. In some cases a numerous brood of young cells is found within the cavity of the parent cell. In lymphatic glands affected in cases of cancer of the stomach and cancer of the rectum, the multiplication of nuclei within the cavity of the parent cell can be observed. It is obviously the same process as that described as follows by Virchow for scrophulous glands:* "In the "lymphatic glands the first stage of the process is a very remarkable "hypertrophy of the elements by endogenous formation of nuclei. While "the cells increase in size five or six times, one sees that the nuclei "multiply in pairs, probably by a division pairwise, so that as many as "twelve pairs of various size may be counted in the same cell." It may be mentioned that the largest number of endogenous nuclei in single cells occurred, in the present series of preparations, in a case of secondary tumour in the lung of the cat, after cancer of the breast. The cells lay within the lung alveoli, and appeared to be the swollen cells of the alveolar epithelium. A large endogenous brood is however the exception. The most common case is where the vacuolated cell carries an oblong or crescentic nucleus-like body on one side. It is this body, becoming disengaged, that forms the tumour element. Now, the vacuolation or endogenous process is sufficiently characteristic to be traced. It is first seen in large protoplasmic cells lying in the lymph sinuses; it is then seen in groups of the same cells at scattered points in the midst of a follicle; and lastly it is seen all over the follicle. In the last-mentioned stage it is quite obvious that the cells generally undergoing the vacuolation process are none other than the enlarged lymphoid cells themselves. The lymphoid cells swell up, become granular and vacuolate, and thus the transformation into tumour cells becomes general.

An interesting question now arises, Do all the cells that are seen in the infected lymphatic gland undergoing the vacuolation process, belong to the pre-existing elements of the gland, or are some of them conveyed to the gland from without? Again, if there are foreign cells among them, how are they distinguishable from, and what is their relation to, those cells of the part that undergo the same process? It is here that it seems possible to reconcile the discrepancies in the different accounts of lymphatic gland infection.

As regards the lymphatic glands infected from mammary tumours in the bitch, it is possible to speak definitively on the point now at issue, for the large round cells filled with yellow or brown pigment have been shown by me in my last report to be normal waste products of the mammary secretion. In health those waste products are conveyed to the lymphatic gland and are there disposed of; in disease they are conveyed to the lymphatic gland and play a conspicuous part in the infective process. Their agency in carving out the pattern of the primary tumour from the swollen substance of the lymphatic gland has been already described. Leaving the mammary cases for a time, let us consider cases of the stomach and intestine as illustrating a variety of the process. In the affected lymphatic glands in cases of cancer of the stomach and cancer of the rectum there are found cells exactly analogous to the large yellow cells in the mammary cases in the bitch. Those cells are not tumour cells, any more than the large yellow cells are tumour cells. They are large rounded cells, with the peculiar protoplasm of the secreting

* *Würzburger Verhandlungen*, Vol. I., 85.

epithelium of the stomach. They are the waste products of the secretion of the stomach, in the same way that the large yellow cells are waste products of the mammary epithelium. It is of such epithelial waste cells, or waste products of the secretion, that epithelial tumours are composed; and the cells that are conveyed to the lymphatic gland are not tumour cells, but cells of the primariiy diseased part, which, if they had remained in their habitat, would have become tumour cells. They would have become elements of the primary tumour after undergoing a more or less obvious transformation, and they become elements of the secondary tumour by fulfilling the same destiny in their new abode. So far, there is no infection, but a mere change of locality. But their presence in the lymphatic gland leads to a transformation of the cells among which they lie. Whenever they overflow into the follicles, the cells of the follicle begin to undergo the tumour transformation. Now, there are two very instructive varieties in this process which have been adverted to already. In the one, the foreign cells overflow, and are the agents of carving out or determining the exact copy of the primary tumour. This they do by becoming vacuolated and leaving a space in their room, the cells of the lymphatic gland undergoing all the while a direct or non-vacuolar transformation. The foreign cells contribute nothing to the new growth, except its form. The other variety is in striking contrast to this. The foreign cells overflow into the follicles, and there, as well as in the lymph-sinuses, they undergo that endogenous process by which they become the elements of the new growth. They induce the same endogenous process in the lymphoid cells near them, and both contribute *pari passu* to the building up of the substance of the new growth. In this case there is direct vacuolation of every single cell; but in the other case the vacuolation takes place only in the foreign cells, and it may be said to be done by them *vicariously* for the cells of the part. In the one case, also, the initial parenchymatous swelling of the lymphatic follicle took place all over the gland at once; but in those cases where the individual vacuolation of the follicular cells is observed, the parenchymatous swelling appears to break out in limited zones or islands of the gland, and to be in fact the immediate precursor of the vacuolation process in each cell.

The simplest mode of infection may therefore be said to be that in which a considerable number of cells are conveyed from the primarily diseased part to the lymphatic gland, where they themselves undergo a transformation to tumour cells, and at the same time induce, by contact or by some other unknown influence, a similar transformation in the proper cells of the part. The case of gonorrhœal pus conveyed to the conjunctiva and setting up a purulent formation there, is rougly analogous. The analogy cannot be pushed far, as the conditions of an expanse of mucous membrane are different from those of a parenchymatous organ. The analogy, however, holds good to this extent, that as gonorrhœal pus produces gonorrhœal pus, so tumour cells produce tumour cells. Gonorrhœal inflammation is morphologically a simple process, while a tumour process implies the formation of a more or less complex organoid growth.

The mode of infection that comes next in complexity and in obscurity is where a few cells overflow into the lymphatic parenchyma, and determine the transformation of all the cells of the part within a certain radius. There are two instructive points of difference between this case and the last. The few cells that are the agents of infection do not appear to contribute to the substance of the secondary formation, and the cells of the part which alone form the new growth, do not, in some cases at least, undergo the characteristic endogenous transfor-

mation. But the few infecting cells undergo this transformation, and they may be said to do so vicariously for the cells of the part. Through the efficacy of the imported cells, the lymphoid cells of the lymphatic gland assume more or less directly the structure of the primary tumour. Now, it is this direct transformation of the secondary parenchyma into the likeness of the primary tumour that is characteristic of some of the most malignant or intense tumour infections, and it may be said to distinguish sarcomatous tumours as a class, where those tumours do have the lymphatic glands affected. In such cases it is difficult to trace any transport of infecting cells. The whole parenchyma appears to transform itself directly into the likeness of the parent tumour, as if through some unseen and inscrutable agency. But that agency need not be assumed to differ in kind from the so-called vicarious agency of certain cells in other cases. If a few cells originating in, and physiologically belonging to, the primarily diseased part, can determine the transformation of a lymphatic gland by being conveyed to it, but without contributing by their own substance to its new structure, then it is conceivable that a similar influence may operate on the lymphatic parenchyma from a still greater distance, that is to say, from the original habitat of the cells in the primarily diseased part. Certain it is that in tumour-infection we are warranted in assuming no other agency than is contained among the properties of the cell, however obscure those properties may be. The occult influence of the spermatic cells is a mystery large enough to cover all the varieties of infective influence residing in cells, and to make them seem intelligible by comparison. But the problem of tumour-infection presents more points of attack than does the mystery of generation. The spermatic influence is, in its effect, one and indivisible, while the infective influence of parent tumours may vary infinitely in degree. It is from such of those variations as have come under notice in the present research that a certain amount of explanation appears to have been reached. In the simplest form, glandular cells of the mamma or the stomach which would have in time contributed to the primary new growth are conveyed, by the physiological channel, to the lymphatic gland; in their changed situation they not only fulfil their destiny and become tumour cells, but they induce a like transformation in lymphoid cells that they come in contact with. In the next degree, the conveyed cells exert a wider and more direct influence on the lymphatic parenchyma; by their agency the pattern of the primary tumour is carved out of the lymphatic gland. In the least intelligible class of cases, the influence is still more widely diffused and more direct, and is indeed invisible except in its effects. But it is as clearly derived from the primary tumour as in the former cases; for the lymphatic gland puts on the likeness of the primary tumour even to the most minute particulars. In this extreme form of infection, no transport of entire cells can be traced; but we do not therefore seek for an explanation of the infection outside the properties of the cell. Virchow, in treating of purulent infection, was led to think that the infectiveness was inherent not in the forms of cells but in the fluids that are present in or about the cells, and Billroth, in speaking of cancerous infection in the passage already quoted, thought that the infectiveness might reside in the "serum or intercellular substance."

One point remains to be noticed. In the growth of a secondary tumour, whether in a lymphatic gland or in an organ like the liver, there is not merely a resemblance between the individual tumour cells of the secondary nodule and those of the primary tumour, but there is the most remarkable resemblance in the arrangement of the stroma and in the general conformation of the growth. The infection implies not

only a transformation of the cells of an infected area into the likeness of cells of the primary tumour, but it implies also a consensus or co-operation among the elements of the infected part to assume the grouping and general plan of the primary tumour. Nothing can be more striking than to find that a lymphatic gland infected from a sarcoma growing from periosteum, acquires the appearance as if its own sarcomatous cells had grown interstitially within, or from the germinal surface of a periosteal tissue. Yet the mimicry of the infective process is as complete as that. The primary tumour, if it is in an epithelial organ, can be accounted for rationally by following out the functional aberrations of the organ or part, and if it grows from a tissue like periosteum, it can be rationally explained as a departure from the cellular laws of nutrition or of growth. The ultimate form of the primary tumour, one may say, is very much a matter of chance ; its design is not predetermined, but it is developed step by step, and it may vary according to circumstances. But in the secondary growth there is present from the beginning of the process a fully prepared design, which is followed as if implicitly. The primary tumour is the result of natural laws and their aberrations; but the secondary tumour is the result as if of a single creative fiat.

Thus, although the primary tumours of the breast are rationally to be considered as nothing else than diseased breasts or parts of the breast, which are still, to a certain extent, identical with or continuous with that organ of the body both structurally and functionally, yet from the point of view of their infectiveness, those tumours manifest an autonomy or individuality which entitles them to be considered as separate existences. But that individuality is not for every tumour of the breast one and indivisible ; or it should rather be said that a tumour of the breast is not always one and indivisible. It is a diseased process extending to more or less of the mammary structure ; but the issue of the diseased process is not necessarily the same at all points where the process is in force. In the first of the group of four cases described above, there were two kinds of secondary structure found in two different lymphatic glands. One of these wore the form of papillary outgrowths as if from the walls of acini, and the other resembled a collection of smaller acinous spaces lined with cubical epithelial cells with large nuclei. Now corresponding differences were found in different parts of the diseased mammary tissue, as they are indeed constantly found in the various centres of disease in the widely-extended mamma of the bitch. Each of those centres can be a source of infection and the case that has been referred to proves that such centres may exist quite close to each other and may each infect with its own type of structure different lymphatic glands lying in the same packet. That fact does not perhaps carry the analysis of the tumour-infective process much farther than it was before; but it appears to be a well-established fact, and has to be taken account of.

No. 6.

Further Researches on the Chemical Constitution of the Brain.

By J. L. W. Thudichum, M.D.

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I.—CONTINUATION OF THE STUDY OF THE PHOSPHORISED PRINCIPLES.

1. Chemolysis of Kephaline.

In the previous research (Rep. No. III., 1874, pp. 138 to 146,) it was found that when kephaline was boiled during some time with a solution of caustic soda or baryta, it was split up into simpler nuclei, which varied according to the nature of the alkali and the duration of its action. A preliminary description of these products was given, and it was proved that the phosphorus contained in kephaline was present in the form of *glycerophosphoric acid.* The baryum salts of *two fatty acids* were obtained, of which the one was soluble in ether, the other insoluble. But the nature of the *radicle containing the nitrogen* of kephaline was not elucidated, probably because the influence of the fixed alkalies destroyed the nitrogenised base almost as quickly as it was formed, so that ammonia and a small quantity of a nitrogenised base containing carbon were the only representatives of the presumably more complicated body. The chemolytic experiments on kephaline were therefore continued in a variety of ways, described in the following :—

Decomposition of Kephaline by Dilute Hydrochloric Acid.—The acid was chosen because it was hoped that it would fix the base when

once formed, and not allow it to be further chemolysed by heat and water. But this expectation was disappointed, as the acid solution, after some hours of boiling, yielded only ammonia, and no compound nitrogenised base; some glycerophosphoric acid was also isolated. The other products insoluble in water formed a mass, which, oily while hot, became solid on cooling, and was mainly a mixture of the fatty acids already alluded to. They dissolved, with the aid of ammonia, in hot water, and then furnished baryta salts, with barytic chloride, of which one portion was soluble in ether. This *soluble in ether* baryum salt was decomposed by means of ether and hydrochloric acid; the acid was again dissolved in ammonia water and transformed into a lead compound. This lead salt was also soluble in ether and contained 22·278 °/₀ of Pb. The portion of the *baryum salts insoluble in ether* was also transformed into lead salts, and was found to consist of *two lead salts*, of which the one was soluble, the other insoluble in ether. It was thus evident that the chemolysis by hydrochloric acid offered no advantages over the methods previously tried, and it was therefore not repeated.

Chemolysis of Kephaline Cadmic Chloride by Baryta.—In this experiment two sets of baryum salts were again obtained, one *soluble*, the *other insoluble in ether*. The salt which was soluble in ether furnished a lead salt, which was likewise soluble in ether (28·056 °/₀ Pb.), and insoluble in, and precipitated by, ether-alcohol. The salt which was insoluble in ether, when transformed into lead salt, was found to consist of two compounds, one insoluble in ether and in alcohol, the other soluble in ether, but precipitated from it by the addition of alcohol.

The barytic solution was freed from excess of baryta by carbonic acid, and the filtrate, after evaporation to a low bulk, was treated with absolute alcohol. A precipitate of barytic glycerophosphate was obtained, and identified by quantitative analysis. The alcoholic mother liquor was neutralised with hydrochloric acid, and precipitated with platinic chloride. The platinum salt so obtained was recrystallised from water, and ultimately obtained in brilliant plates and needles.

Analyses :—

(*a.*) 0·6760 grm. gave 0·2178 grm. platinum, and 0·9332 grm. argentic chloride =32·219 °/₀ platinum and 34·149 °/₀ chlorine.

(*b.*) 0·5454 grm. gave 0·396 grm. CO_2 and 0·232 grm. H_2O = 19·801 °/₀ C and 4·726 °/₀ H.

(*c.*) 0·463 grm. gave 16·3c.c. normal nitrogen = to 4·404 °/₀ N.

Computation of Analyses :—

	Per-centages.	÷ At. Wgts.	÷ Pt = 1.
C	19·801	1·650	10·1
H	4·726	4·726	29·0
N	4·404	·314	1·9
O	4·701	·293	1·8
Pt	32·219	·163	1·0
Cl	34·149	·961	5·9

$= (C_5 H_{13} N O)_2 (H Cl)_2 Pt Cl_4$.

Neurine hydrochlorate platinic chloride, or $(C_5 H_{14} N O Cl)_2 Pt Cl_4$.

Besides the above salt, there was obtained from the alcoholic mother liquor from which it had been originally precipitated, a smaller quantity of a second crystallisable platinic salt. After recrystallisation from water it gave the following numbers on analysis :—

(*a.*) 0·3840 grm. gave 0·141 grm. Pt and 0·610 grm. Ag Cl = 36·718 °/₀ platinum and 39·297 °/₀ chlorine.

(*b.*) 0·7266 grm. gave 0·244 grm. CO_2 and 0·205 H_2O = 9·158 °/₀ C and 3·134 °/₀ H.

(*c.*) 0·6234 grm. gave 27 c.c. N normal = 5·418 °/₀ N.

Computation of Analyses :—

	Per-centages.	÷ At. Wgts.	÷ Pt = 1.
C	9·158	·763	4·1
H	3·134	3·134	16·8
N	5·418	·387	2·0
O	6·275	·392	2·1
Pt	36·718	·186	1·0
Cl	39·297	1·107	5·9

$= (C_2 H_7 N O)_2 (H Cl)_2 Pt Cl_4$, or $(C_2 H_8 N O Cl)_2 Pt Cl_4$.

This salt might be considered as dimethylamine, in which the third atom of hydrogen is replaced by hydroxyle, or as oxethylamine simply

$$\left.\begin{matrix} C_2 H_5 O \\ H \\ H \end{matrix}\right\} N$$

that is to say, a body formed from neurine, by the loss of three radicles of methyle and one of water.

A third base was also obtained ; it was soluble in alcohol as platinic salt, giving the solution a brownish red colour, and on the addition of much ether was precipitated. It was purified by repeated solution in alcohol and reprecipitation by ether. Several grammes of this body which was precipitated in an oily state, but became solid on drying, were obtained. It was dried at 100° C. and analysed :—

(*a.*) 0·5392 grm. gave 0·2128 grm. Pt. and 0·7884 grm. Ag Cl = 39·466 °/₀ Pt. and 36·171 °/₀ Cl.

(*b.*) 0·5718 grm. gave 0·2520 grm. CO_2 and 0·168 grm. H_2O = 12·019 °/₀ C and 3·070 °/₀ H.

(*c.*) 0·4486 grm. gave 20 c.c. N at 15° C. and 749 mm. K H O col. = to 11·6 m.m. mercury = 5·019 °/₀ N.

Computation of Analyses :—

	Per-centages.	÷ At. Wgts.	÷ Pt
C	12·019	1·001	5·0
H	3·070	3·070	15·3
N	5·019	·358	1·79
O	4·255	·265	1·3
Pt	39·466	·20	1·0
Cl	36·171	1·018	5·0

leading to a formula $C_5 H_{14} N_2 O$, H Cl, Pt Cl_4. This body, so anomalous in its constitution, has probably been derived from neurine molecules by duplication and subsequent decomposition. Such a condensation is observed upon the neurine molecules under the influence of oxydising agents.

Chemolysis of Kephaline by Baryta, with the view of identifying the base only.—The process was the same as in the former experiment. The platinum salt gave on analysis the following results :—

(*a.*) 0·5975 grm. gave 0·1902 grm. Pt and ·8282 grm. Ag Cl = 31·832 °/₀ Pt and 34·290 °/₀ Cl.

(*b.*) 0·5132 grm. gave 0·3760 grm. CO_2 and 0·2180 grm. H_2O = 19·981 °/₀ C and 4·719 °/₀ H.

(*c.*) 0·4438 grm. gave 16·8 c.c. N normal = 4·735 °/₀ N.

Computation of Analyses:—

	Per-centages.	÷ At. Wgts.	÷ Pt = 1.
C	19·981	1·665	10·3
H	4·719	4·719	29·3
N	4·735	·338	2·0
O	4·443	·278	1·7
Pt	31·832	·161	1·0
Cl	34·290	·966	6·0

$= (C_5 H_{13} N O)_2 (H Cl)_2 Pt Cl_4$, or $(C_5 H_{14} N O Cl)_2 Pt Cl_4$.

Decomposition of Kephaline by Baryta.—This experiment was undertaken upon a larger amount of kephaline than the previous ones. The kephaline was first warmed in water, whereby it swelled and dissolved to a paste, which was then boiled with two molecules of $Ba H_2 O_2$ in the ordinary way.

The baryum salts obtained in the earlier experiments were again found, and it was moreover observed that one of the fatty acids contained in them gave the purple reaction, which cerebrine also gives with sugar and sulphuric acid, and which resembles Pettenkofer's test for biliary compounds.

From the solution drawn off from the baryum salts of the fatty acids the excess of baryum was removed by $C O_2$, and the resulting filtrate concentrated by evaporation, and then treated with alcohol. The glycerophosphate of baryum thus obtained was converted into lead salt, and the lead salt into calcium salt ($C_3 H_7 Ca P O_6$).

The alcoholic mother liquor was freed from alcohol by evaporation, and the resulting solution after addition of nitric acid was precipitated by phospho-molybdic acid, and the product decomposed by hot $Ba H_2 O_2$. The yellow filtrate freed from the baryum that admitted of removal by $C O_2$, did yet contain baryum in combination. This was proved by combustion of the dried salt and analysis of the residue.

The concentrated solution of the base was freed from Ba by an equivalent amount of very dilute sulphuric acid, then neutralised by hydrochloric acid, and precipitated after concentration by alcoholic $Pt Cl_4$. The precipitate was recrystallised from water, 10 grammes being obtained in the shape of crystallised plates. The salt was dried and analysed:—

(*a.*) 0·910 grm. gave 0·299 grm. Pt and 1·2634 grm. Ag Cl = 32·85 °/₀ Pt and 34·34 °/₀ Cl.

(*b.*) 0·4770 grm. gave 0·3406 grm. $C O_2$ and 0·2130 grm. $H_2 O$ = 19·47 °/₀ C and 4·94 °/₀ H.

(*c.*) 0·0340 grm. gave by combustion in vacuo with Cu O and copper, 14·1 c.c. total gas normal. Of this 13 c.c. were $C O_2$ and 1·1 c.c. were N = to 4·04 °/₀ N.

Computation of Analyses:—

	Per-centages.	÷ At. Wgts.	÷ Pt = 1.
C	19·47	1·622	9·7
H	4·94	4·94	29·7
N	4·04	·288	1·7
O	4·36	·272	1·6
Pt	32·85	·166	1·0
Cl	34·34	·967	5·8

$= (C_5 H_{13} N O)_2 . (H Cl)_2 Pt Cl_4$, or $(C_5 H_{14} N O Cl)_2 Pt Cl_4$.

The alcoholic motherliquor from which this salt had been precipitated gave by precipitation with ether a quantity of the fluid oily salt, the

analysis of which has been given in a former paragraph ($C_5 H_{14} N_2 O$) $H Cl Pt Cl_4$, but it was very small in amount.

A third base was also obtained in small quantity by simple addition of much nitric acid to the original solution, after removal of glycero phosphate, and before precipitation with phospho-molybdic acid, and which gave the various alkaloidal tests.

Summary of results obtained in the various Chemolyses of Kephaline.—Kephaline may be regarded, considering its elementary composition and the products of its chemolysis, as a body in which two hydroxyls of the glycerine molecule are replaced by fatty acids (in part hitherto unknown), and in which the third hydroxyl is replaced by phosphoryl, which latter in its turn has one hydroxyl replaced by an ammonium base, thus :—

$$C_3 H_5 \begin{cases} \text{Fatty acid} \\ \text{Fatty acid} \\ H O (O P O) C_5 H_{13} N O. \end{cases}$$

The whole of the phosphorus is apparently contained in the radicle of glycerophosphoric acid, and in no other form. This body is first obtained on chemolysis, but being somewhat unstable, it is not difficult in the presence of bases to decompose it further into glycerine and phosphate of the base used.

The whole of the nitrogen appears to be present as neurine; the other bases which have been obtained being probably derived from neurine by secondary changes. This secondary decomposition would explain why the amount of the neurine obtained from a given weight of kephaline is less, sometimes much less, than the amount which they would lead us to expect.

Of the fatty acids contained in kephaline, various baryum, lead, and magnesium salts have been examined and analysed; but the results obtained do not yet justify the attempt of explaining their intimate relations. It is highly probable that the acid contained in the main soluble in ether, baryum, or lead salt, belongs to a series of acids containing at least one atom of oxygen more than the ordinary fatty acids; it possesses a power of absorbing oxygen, which makes its chemical manipulation a matter of the greatest difficulty.

**Note of an Essay on Glycero-phosphoric Acid and its Salts as obtained from the phorphorised Constituents of the Brain.*—The details of the data concerning glycerophosphoric acid from kephaline and other sources evolved in the course of this process, and certain additional matters, were communicated to the Chemical Society in a paper entitled : *On Glycero-phosphoric Acid and its Salts, as obtained from the phosphorised constituents of the Brain. By J. L. W. Thudichum and C. T. Kingzett*, printed in the second volume for 1876 of the Journal of the Chemical Society, p. 20, et seq. The paper consists of nine paragraphs. Of these the first contains an historical note; (2) a description of lead glycerophosphate; (3) a description and several analyses of normal glycerophosphate of calcium ($C_3 H_7 Ca P O_6$); (4) a description and analysis of acid glycerophosphate of calcium ($C_6 H_{16} Ca P_2 O_{12}$), here described for the first time; (5) glycerophosphate of baryum ($C_3 H_7 Ba P O_6$) from synthetically prepared acid, and from brain matters; also a hydrate, precipitated by alcohol ($C_3 H_7 Ba P O_6$, $H_2 O$); (6), the alcoholo-hydrated barytic glycerophosphate, containing probably at least three molecules of alcohol and six of water combined with one molecule of acid glycerophosphate; (7) In this paragraph the extraordinary features of this salt, which is new to

science, are compared with a few similar bodies known to science ; but the authors say : " Glycerophosphate of baryum not only seems to be " the only organic compound which is known to form alcoholates, but " it is in so far unique (amongst inorganic and organic bodies) as it " forms a compound which is *an alcoholate* and *a hydrate* at the same time ;" (8) is analytical, and relates to the instability of some glycerophosphates and the difficulty of burning their carbon entirely ; (9) is a theoretical summary, exhibiting the constitution of the simplest phosphorised principles of the brain by the aid of four different formulæ.

2. Chemolysis of Amido-Myeline.

The body which formed the material for the following investigation was described in Report for 1874, No. III., new series, p. 179, as myeline cadmic chloride, and on analysis had given figures which led to the formula $C_{84} H_{165} N_3 P_2 O_{18}, 2 Cd Cl_2$. It was there stated that it was possible or necessary to assume that it was a mixture or compound in atomic proportions of two bodies, one of which contains only one atom of N, while the other contains two atoms of N.

The process.

The compound on being placed in water swelled to a solid white jelly. It was then mixed with a solution of baryta containing what was calculated to be equal to three equivalents of the hydrate. The mixture was now boiled in a platinum still, with the view of condensing any volatile products, and collecting them in acidulated water. The boiling was continued during about 12 hours. There were obtained three different sets of products, (A) the baryum salts of several fatty acids, together with cadmic oxyde; (B) a solution of products containing nitrogenised matters, glycerophosphate and chloride of baryum ; (C) a distillate combined with acid.

Products.

(A.) *The Baryum Salts of the Fatty Acids.*—They were decomposed with dilute hydrochloric acid in the presence of ether, and gave a dark-coloured ethereal solution (*a*) and a matter which assumed a gelatinous condition and remained insoluble (*b*).

(*a.*) *Examination of the Ether Extract.*—It was washed with water and distilled to dryness, the residue was dissolved in ammonia and much water. The hot filtrate was treated with solution of lead, whereby the acids were precipitated as lead salts. These were dried and treated with ether, when a white portion remained insoluble, while a coloured portion dissolved.

(*α.*) *The Soluble Lead Salts* were again decomposed by hydrochloric acid and ether, and then tranformed into baryum salts. On extracting these with ether, the greater part was found soluble in this agent, while a small portion remained insoluble and had a white colour.

(*α* 1.) *Insoluble* (*in Ether*) *Baryum Salt from Soluble* (*in Ether*) *Lead Salt.*—It was decomposed with hydrochloric acid, and furnished a fatty acid fluid below 25° C. It was reconverted into baryum salt, and this was boiled with alcohol. A portion dissolved, another portion remained insoluble in the boiling alcohol.

Portion Soluble in Boiling Alcohol.—The salt was deposited from the alcohol on cooling, and after drying at 100° C. it was analysed.

(*a.*) 0·343 grm. gave 0·117 grm. $Ba S O_4 = 20·05$ °/₀ Ba.

(*b.*) 0·3834 grm. gave 0·8352 grm. Co_2 and 0·3334 grm. $H_2 O =$ 59·411 °/₀ C and 9·662 °/₀ H.

Computation of Analyses :—

	Per-centages.	÷ At. Wgts.	÷ Ba = 1.
C	59·41	4·95	33·9
H	9·66	9·66	66·1
Ba	20·05	·146	1·0
O	10·88	·68	4·6

These figures approach the theory relating to margarate, 2 ($C_{17} H_{33} O_2$) Ba ; but this compound is excluded by the solubility in boiling alcohol of the salt, and the low fusing point of the free acid. These features point indeed to oleic acid and oleate, but this is incompatible with the result of the analysis. The acid could not have been a homologue of oleic acid, on account of the deficiency of the oxygen. The analyses exhausted the whole quantity in hand, which did not exceed one gramme. The study of this body must therefore be resumed on a future occasion.

Portion Insoluble in Boiling Alcohol.—This salt fused in the boiling alcohol, but did not dissolve. After decomposition with acid and ether it yielded a fatty acid which fused at 18°, and on cooling became solid again at 17° C. The quantity of this body obtained was too small for analysis.

(α 2.) *The Soluble in Ether Baryum Salt* was precipitated from the ether by 85 °/₀ alcohol, and it was then redissolved and reprecipitated. Washed and dried at 100° C.

(*a.*) 0·5954 grm. gave 0·1446 grm. Ba S O_4 = 14·27 °/₀ Ba.

(*b.*) 0·3124 grm. gave 0·7274 grm. Co_2 and 0·2752 H_2O = 63·502 °/₀ C and 9·787 °/₀ H.

Computation of Analyses :—

	Per-centages.	÷ At. Wgts.	÷ B = 1.
C	63·502	5·2918	50·88
H	9·787	9·787	94·1
Ba	14·270	·104	1·0
O	12·441	·777	7·4

leading to the formula 2 ($C_{26} H_{47} O_4$) Ba. After this analysis the salt was again decomposed by H Cl and the free acid examined. It was solid at 18°, became softer between 25° and 30°, at 30° it was more mobile, and at 39° it entirely fused to a clear but coloured oil.

It was now converted into $N H_3$ salt, and this was transformed into lead salt, which was precipitated from its ethereal solution by alcohol and the dark salt again analysed.

(*a.*) 0·3858 grm. gave 0·6720 grm. C O_2 and 0·255 H_2O = 47·50 °/₀ C and 7·34 °/₀ H.

(*b.*) 0·2316 grm. gave 0·1106 grm. Pb S O_4 = 32·62 °/₀ Pb.

Computation of Analyses :—

	Per-centages.	÷ At. Wgts.	÷ Pb = 1.
C	47·50	3·958	25·2
H	7·34	7·34	46·7
Pb	32·62	·157	1·0
O	12·54	·783	4·9

leading to the formula $C_{26} H_{46} O_5$ Pb. During the transformation the acid had perhaps absorbed some oxygen, or had taken up a molecule of water and become dibasic. This increase of the basicity might also be a function of the lead, which has a great tendency to form basic compounds. For the purposes of the following considerations we may assume the acid to have had the formula $C_{26} H_{48} O_4$ or $C_{25} H_{48} O_5$. With sugar and sulphuric acid it gave the reaction characteristic of biliary acids, namely a deep purple colour.

By its composition also this acid approaches to and stands intermediate between certain biliary compounds, such as cholic acid cholesterine, and

Cholesterine	$C_{26} H_{44} O$
Myelocholic acid	$C_{26} H_{48} O_4$ (in baryum salt)
	$C_{26} H_{48} O_5$ (in lead salt)
Psychosine	$C_{25} H_{49} O_8 N$ (see below)
Cholic acid	$C_{24} H_{40} O_5$

This relation is all the more striking as cholesterine, named from the bile, of which it is a normal ingredient, is also an ingredient of the brain, and that in much larger quantities than those in which it is found in the bile. But the comparison of quantities is of little value, as long as the function of the substance is not ascertained. The first aspect of these relations will, however, justify us in terming this new acid *myelocholic acid.*

(*β.*) *The lead salt insoluble in ether.*—This was again decomposed by hydrochloric acid in the presence of ether, and the colourless ethereal solution on distillation left a fatty acid fusing about 62—64° C. It was washed by successive meltings over pure water, and then by recrystallisation from dilute alcohol. This proceeding gave a large crop of wart-like crystals.

(*a.*) 0·1530 grm. gave 0·417 grm. CO_2, and 0·180 grm. H_2O = 74·33 °/₀ C and 13·06 °/₀ H.

Computation.

	Per-centages.	÷ At. Wts.	÷ 0 = 1.	
C	74·33	6·1941	7·87	×2
H	13·06	13·07	16·6	×2
O	12·61	·787	1·0	×2

$= C_{16} H_{32} O_2$

This analysis and its fusion point prove the acid to have been palmitic.

B. *Examination of the Solution filtered from the Baryum Salts of Fatty Acids.*

(*a.*) The excess of baryta was removed by CO_2, the filtrate concentrated and precipitated by alcohol. *The precipitate* consisted of chloride and glycerophosphate of baryum. These were separated by suitable means, and several salts of the glycerophosphoric acid prepared and analysed. Thus 0·3736 grm. of the normal calcium salt gave 0·2264 grm. $Ca_2 P_2 O_7$ on ignition = 60·59 °/₀ calcium; theory requires 60·47 °/₀ Ca.

(*β.*) *The alcoholic solution* was freed from alcohol by evaporation, rendered acid, and precipitated by phospho-molybdic acid. The precipitate so obtained was then decomposed with hot baryta water; the excess of baryum was removed by CO_2, and the resulting solution after neutralisation with hydrochloric acid was evaporated to dryness on a water bath. On extracting the residue with absolute alcohol baric chloride remained insoluble, while the alcoholic filtrate gave with platinic chloride a yellow salt which was recrystallised from water. These crystals were thin rhombic plates, and on analysis gave the following numbers:—

Isolation of the alkaloid.

(*a.*) 0·471 grm. gave 0·3304 grm. CO_2, and 0·198, H_2O = to 19·131 °/₀ C and 4·67 °/₀ hydrogen.

(*b.*) 0·7746 grm. gave 0·2506 grm. Pt and 1·0836 AgCl = 32·352 °/₀ Pt and 34·636 °/₀ Cl.

(*c.*) 0·0536 grm. gave by combustion in vacuo with CuO and copper, 1·8 c.c. N normal, showing 4·201 °/₀ N.

Computation of analyses:—

	Per-centages.	÷ At. Wgts.	÷ Pt. = 1.
C	19·131	1·5942	9·7
H	4·670	4·670	28·6
N	4·201	·300	1·8
O	5·140	·321	1·9
Pt	32·252	·163	1·0
Cl	34·606	·974	6·0

$= (C_5 H_{13} N O)_2 (H Cl)_2 Pt Cl_4$ or $(C_5 H_{14} N O Cl)_2 Pt Cl_4$.

C. *Examination of the Distillate from the Chemolysis.*

(α.) The distillate was strongly alkaline and had an odour of trimethylamine; it was redistilled and the product neutralised with very dilute sulphuric acid. This solution was evaporated to dryness on the water bath, and on extraction with absolute alcohol, there was left an insoluble white salt, which when dry weighed less than 1 grm., and was proved by analysis to consist of sulphate of ammonium.

0·0218 grm. dried at 80° C. gave by combustion in vacuo with oxyde of copper and metallic copper, 3·70 c.c. N normal = 21·23 °/₀ N; theory requires 21·21 °/₀.

β. *The alcoholic extract* gave with alcoholic $PtCl_4$ a small quantity of salt, which was recrystallised from water, and weighed when dry less than 0·5 grm. It was probably the platinum salt of a volatile base.

The products which have been described in the foregoing may be considered as the more simple products of the chemolysis; some of them, such as the fatty acids, are final, inasmuch as they cannot be changed by a continued influence of the alkali under the same conditions. Others, such as the glycerophosphoric acid, would change but little by continued action of excess of baryta; the nitrogenised body, however, would be entirely destroyed by a long continuance of this influence. It is therefore necessary to interrupt the process before any newly-formed nuclei are entirely destroyed, and this entails the necessity of leaving some portions of the original matter imperfectly chemolysed. Of this kind was the matter which when the baryta salts of the fatty acids were decomposed by hydrochloric acid and water in the presence of ether, remained suspended in the water as a gelatinous mass. (*See* A *b*.)

Differentiation the gelatinous mass. Three new bodies.

(b.) *The gelatinous mass* just alluded to was found to consist of four different bodies, which were separated from each other in the following manner. It was dissolved in hot alcohol; this deposited a crystalline body on cooling (α β and γ), and kept another in solution δ. The matter recrystallised from alcohol was again treated with hot alcohol, and now it did dissolve only partially; that which dissolved was re-precipitated on cooling, whilst that which did not dissolve fused like stearoconote.

(α.) *Analysis of deposited matter after drying at* 80° C.:

(a.) 0·0238 grm. gave by combustion in vacuo with Cu O and Cu 0·39 c.c. N normal = 2·05 °/₀ N.

(b.) 0·3334 grm. gave 0·8562 grm. CO_2 and 0·3616 grm. H_2O = 70·03 °/₀ C and 12·04 °/₀ H.

(c.) 1·0374 grm. gave 0·1222 grm. $Mg_2P_2O_7$ = 3·289 °/₀ P.

Computation of analyses :—

	Per-centages.	÷ At. Wgts.	P = 1.
C	70·03	5·836	55·0
H	12·04	12·04	113·0
N	2·05	0·146	1·3
P	3·289	0·106	1·0
O	12·591	0·786	7·4

= $C_{55}H_{113}NPO_7$ Palmito-myeline.

Further on we shall return to the study of this substance with the view of elucidating its constitution.

(β.) That part of the matter which fused in the alcohol and remained insoluble was soluble in benzene, from which it was reprecipitated by alcohol as a plastic precipitate.

On placing this in ether part dissolved and part remained insoluble That which remained insoluble (γ) was preserved for investigation in the future ; while the ether solution was precipitated by alcohol in a snow-white flaky form. It was dried at 100° C. and analysed.

(a.) 0·3680 grm. gave 0·7434 grm. $C O_2$ and 0·3196 $H_2 O$ = 55·02 °/₀ C and 9·64 °/₀ H.

(b.) 0·0378 grm. gave 0·6 c.c. N normal (on combustion in vacuo with Cu O and Cu) = 1·98 °/₀ N.

(c.) 0·0285 grm. gave 0·5 c.c. N normal = 2·19 °/₀ N.

(d.) 0·9360 grm. gave 0·178 grm. $Ba S O_4$ = 11·17 °/₀ Ba and 0·1604 grm. $Mg_2 P_2 O_7$ = 4·78 °/₀ P.

Computation of analyses :

	Per-centages.	÷ At. Wgts.	÷ Ba = 1.
C	55·02	4·585	56·5
H	9·64	9·64	118·5
Ba	11·17	0·081	1·0
N	2·08	0·148	1·8
P	4·78	0·154	1·9
O	17·31	1·081	13·3

= $C_{57} H_{118} Ba N_2 P_2 O_{13}$.

This was therefore a salt of baryum which had, probably owing to its peculiar physical condition, escaped decomposition by hydrochloric acid.

(δ.) *Examination of the alcoholic mother liquor :*

The mother liquor from the bodies described under a, β, and γ was concentrated, and made small deposits at various stages, and finally on cooling precipitated a matter which dissolved in ether. The ether solution was mixed with much alcohol, and the solution precipitated by alcoholic lead acetate. The precipitate was washed, isolated, dried at 100° C, and analysed.

(a.) 0·3904 grm. gave 0·323 grm. $C O_2$ and 0·191 $H_2 O$ = 22·566 °/₀ C and 5·435 °/₀ H.

(b.) 0·4904 grm. gave 0·2658 grm. $Pb S O_4$ = 36·65 °/₀ Pb and 0·1214 grm. $Mg_2 P_2 O_7$ = 6·843 °/₀ P.

Computation of analyses :—

	Per-centages.	÷ At. Wgts.	÷ Pb 1.
C	22·566	1·8805	10·6
H	5·435	5·435	30·7
Pb	36·650	·177	1·0
P	6·843	·220	1·2
O	28·506	1·781	10·0

leading to the formula $C_{11} H_{30} Pb P O_{10}$.

Secondary chemolysis of $C_{55} H_{113} N P O_7$ (palmito-myeline).

A quantity of this intermediate product was made into a thin paste with water, and two equivalents $Ba H_2 O_2$, and the whole heated to 130° C. during three hours in a closed platinum tube. Attention was only directed to the solid baryum salts in this experiment, nothing being contained in the baryta solution. They were decomposed with H Cl and ether, and the ether solution decanted and the mother liquor rejected. On now washing the ethereal solution with water a phosphorised matter was obtained as a precipitate. This was isolated, washed, and recrystallised from alcohol, then analysed.

(a.) 0·2458 grm. gave 0·581 grm. CO_2 and O ·2604 grm. $H_2 O$ = 64·46 °/₀ C and 11·77 °/₀ H.

(b.) 0·0434 grm. gave by combustion in vacuo with Cu O and Cu 0·84 cc. N normal = 2·42 °/₀ N.

(c.) 0·6594 grm. gave 0·1000 grm. $Mg_2 P_2 O_7$ = 4·235 °/₀ P.

Computation of analyses :—

	Per-centages.	÷ At. Wgts.	÷ P = 1
C	64·46	5·371	39·4
H	11·77	11·77	86·5
N	2·42	·172	1·2
P	4·23	·136	1·0
O	17·12	1·07	7·8

$= C_{39} H_{86} N P O_8$.

The Ether extract was distilled and the free fatty acid contained in it converted first into ammonium salt, and then into baryum salt insoluble in ether. The latter was then decomposed and the free fatty acid analysed. Its fusion point was near to that of ordinary palmitic acid; 0·1712 grm. gave 0·4400 grm. CO_2 and 0·2000 grm. $H_2 O$ = 70·09 °/₀ C and 12·98 °/₀ H.

	Per-centages.	÷ At. Wgts.	÷ C = 16.
C	70·09	5·840	16
H	12·98	12·980	35·5
O	16·93	1·058	2·9

That is to say it was palmitic acid imperfectly dried before analysis, $C_{16} H_{32} O_2 + H_2 O$.

The two bodies produced by the chemolysis of $C_{55} H_{113} N P O_7$ may have been obtained by this reaction: $C_{55} H_{113} N P O_7 + 3 H_2 O = C_{39} H_{86} N P O_8 + C_{16} H_{32} O_2$. No glycerophosphoric acid or neurine or any other fatty acid resulted from this chemolysis.

Summary of Results.—The body described as amido-myeline, and which had given the formula $C_{84} H_{165} N_3 P_2 O_{18}$, 2 Cd Cl_2 on chemolysis by baryta hydrate has been split up into more simple parts, of which some are intermediate, others ultimate products of the process.

(Aa 1) $C_{17} H_{34} O_2$, *margaric acid*, analysed in the shape of a baryum salt, 2 $(C_{17} H_{33} O_2)$ Ba, and an insoluble (stearoconotised) body.

(Aa 2) $C_{26} H_{48} O_4$, or $C_{25} H_{48} O_5$, *myelocholic acid*, in the shape of a baryum salt, 2 $(C_{26} H_{47} O_4)$ Ba, and in the shape of a lead salt prepared from the baryum salt, of the formula $C_{26} H_{46} O_5$ Pb.

(Aa β) $C_{16} H_{32} O_2$, *palmitic acid*, analysed in the free state.

(B) $C_3 H_9 P O_6$, *glycerophosphoric acid* analysed as calcium salt, $C_3 H_7 Ca P O_6$.

(Bβ) $C_5 H_{15} NO_2$, *choline* or *neurine* analysed in the shape of chloride platinic chloride $(C_5 H_{14} N O Cl)_2 Pt Cl_4$.*

(C) NH_3, *ammonia* analysed as sulphate.

(Cβ) *an organic volatile base*, obtained as chloride platinic chloride, not analysed.

The following were the products which maybe termed intermediate :—

(A b) $C_{55} H_{113} N P O_7$, palmitomyeline; (A b β) $C_{57} H_{118} N_2 P_2 O_{13}$ Ba, a compound which has been examined as baryum salt. (A b δ) $C_{11} H_{32} P O_{10}$, P b, a body which has been analysed as lead salt.

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* The formula of $C_5 H_{15} N O_2$ is rather presumed than proved as regards the exact quantity of the hydrogen and oxygen; for if the H Cl were like the Pt Cl_4 merely an addition, then the formula of the free base would be $C_5 H_{13} NO$; but if the chloride were a product by substitution of hydroxyl by Cl, and expulsion of the hydroxyl as $H_2 O$, then the larger formula for the free body would be correct. Some assume the existence of two bodies of the formulæ which compete in the foregoing consideration and term the one choline or neurine, the other oxycholine or oxyneurine.

The palmitomyeline on secondary chemolysis gave a body—

(A b α 1) C_{39} H_{86} N P O_8, showing a composition very near to the simplest form of myeline. But as it escaped chemolysis by baryta, it is difficult to assume that it should have the intrinsic constitution of this body, and (A b α 2), C_{16} H_{32} O_2, + H_2 O, palmitic acid imperfectly dried before analysis.

We have, therefore, here 12 different bodies, obtained by chemolysis from the primary cadmium salt, of which several are new to chemical science. Some may be assumed to be imperfectly chemolysed intermediate products, or perhaps, but not very probably, bodies formed anew by synthesis. But myelocholic acid is a definite and round radicle, and in that quality becomes a great difficulty in the way of theoretical considerations concerning the structure of the chemolysed compound. I therefore judge it best not to attempt the formation of a structural formula for the amido-myeline cadmic chloride body, but to leave this for a time when the above empirical results shall have been confirmed, amplified, or corrected by repetition and extension.

* *Note of an essay on Hemine, Hematine and a Phosphorised Principle resembling Amido-myeline contained in the Blood.*—The account of this body is given in a research carried out in the Pathological Laboratory, and read before the Chemical Society, and published by that Society in their Journal for September 1876, p. 255 *et seq.*, under the title: *On Hemine, Hematine, and a Phosphorised substance contained in Blood Corpuscles.* By J. L. W. Thudichum and C. T. Kingzett. (Paragraph 1) on the composition of crystallised hemine, fixes the material to have been the one described in the 11th Report of the Medical Officer of the Privy Council, 1869, p. 155, and shows it to have contained 7·6 °/₀ of iron as an essential constituent, nearly 3·°/₀ chlorine, giving no ratio for assuming the compound to be either neutral or basic, and about 0·6 °/₀ phosphorus, showing the crystals to be contaminated with a phosphorised body. (2.) In this section the attempt to saturate the hemine crystals with H Cl is described, and the results are given. (3.) In this paragraph the action of nitric acid on hemine is described, and the statements of Preyer concerning this reaction are refuted. (4.) The action of sulphuric acid on hemine is given, and shown to consist in the production of cruentine, first described in Medical Officer's Report, 1867, p. 228, and 1868, p. 161. The next paragraph (5) describes experiments intended to effect the extraction of iron from hemine, with a view of testing the statements of C. Paquelin and L. Jolly, Comptes Rendus, 79 (1874) 918, to the effect that pure hematine contained no iron. Their processes were first repeated, and then further criticised by experiments. These are given in paragraph (6) action of acetic and citric acids on hemine, and (7) hematine, benzene, and acetic acid. These experiments lead the authors to a very pure hematine, which *contained more iron than has ever before been found in any preparation of hematine*, namely, 9·08 °/₀. The complete analysis of this body leads the authors to the new formula C_{32} H_{32} Fe N_4 O_6 as that of hematine. (8.) In this paragraph the isolation, purification, and analysis of the phosphorised body from the hemine crystals are described. The analyses lead to C_{76} H_{164} N_3 P_2 O_{14} $(Cd\ Cl_2)_2$ and furnish remarkable evidence of the identity of this principle with one obtained from the brain. (Report Medical Officer, New Series, No. III., 1874, p. 174.)

3. Chemolysis of Lecithine.

In my first report on the Chemical Constitution of the Brain (New Series, No. III., p. 180) I pointed out that "lecithine when isolated in

"the only form in which it can at present be separated from the other "brain-matters, namely, as platinic chloride hydrochlorate salt, im- "mediately after isolation begins to decompose, and completes this "decomposition during the steps necessary for its purification." Its platinum salt, which is in the first instance soluble in ether, becomes in the air or in the vacuum speedily covered with oily drops (oleic acid), and the residual salt is then insoluble in ether.

It was upon such changed platinic salt insoluble in ether that the following chemolysis was effected :—

Water alone was found capable of removing at least some of the platinic chloride, but this treatment was not persisted in, and the salt was boiled with two molecules of $Ba H_2 O_2$ during two hours. The decomposition was effected very readily, a black precipitate (of platinum) being formed simultaneously and insoluble baryum salts of certain fatty acids.

Examination of the Baryum Salts.—These were washed with water and then decomposed by hydrochloric acid, in the presence of ether. The ether solution was distilled to dryness and the residual matter converted into ammonium soap, and the latter in its turn was converted into baryum salt once more, and after drying extracted with much boiling absolute alcohol. The alcoholic extraction was continued to perfection.

The extracts deposited a white salt on cooling, which was isolated, dried, and analysed :

(*a.*) 0·1792 grm. dry at 100° C. gave 0·0596 grm. $Ba SO_4$ = 19·55 °/₀ Ba. Oleate of baryum requires 19·59 °/₀ Ba. This salt was therefore *oleate of baryum.*

The baryum salt left undissolved by the alcohol was insoluble in ether. It was once more decomposed by hydrochloric acid in the presence of ether, and converted first into ammonium soap, and again into baryum salt. It was now isolated, dried at 100° C., and analysed :—

(*a.*) 0·1922 grm. gave 0·0648 grm. $Ba SO_4$ = 19·82 °/₀ Ba.

(*b.*) 0·2342 grm. gave 0·4960 grm. $C O_2$ and 0·208 grm. $H_2 O$ = 57·76 °/₀ C and 9·86 °/₀ H.

Computation of Analyses :—

	Per-centages.	÷ At. Wgts.	Ba = 1.
C	57·76	4·813	33·4
H	9·86	9·86	68·4
Ba	19·82	·144	1·0
O	12·56	·785	5·4

$= C_{17} H_{33} ba O_{2·7}$.

This was, therefore, apparently *margarate of baryum*, or a salt of a new acid, $C_{17} H_{34} O_3$, *oxymargaric acid.*

Examination of the Baryta solution.—The excess of baryta was first removed from the solution by means of carbonic acid, and then nitric acid was added to strong acidity. In this state the solution was precipitated by phosphomolybdic acid, and the filtrate reserved. The precipitate was decomposed by hot baryta and concentrated to a low bulk. The baryum which still remained in combination with the base was carefully removed by the exact amount of sulphuric acid necessary, and after concentration the resulting solution was neutralised by H Cl and precipitated by alcoholic $Pt Cl_4$. The platinic compound crystallised from water in long prismatic needles, which proved on analysis to have the same composition as the ammonium base from kephaline, but which crystallised in lustrous plates.

The quantity of the platinum salt obtained was very near to that which should have been obtained, assuming all the nitrogen to exist in one form in lecithine, and to be obtained in one form.

(*a.*) 0·8900 grm. gave 0·2830 grm. Pt and 1·2368 grm. Ag Cl = 31·797 °/₀ Pt and 34·376 °/₀ Cl.

(*b.*) 0·455 grm. gave 0·3158 grm. CO_2 and 0·1920 H_2O = 18·92 °/₀ C and 4·68 °/₀ H.

(*c.*) 0·0324 gave by combustion in vacuo with CuO and copper 1·2c.c. N normal = 4·63 °/₀ nitrogen.

Computation of Analyses:—

	Per-centages.	÷ At. Wgts.	÷ Pt – 1.
C	18·92	1·576	9·78
H	4·68	4·68	29·00
N	4·63	·330	2·00
O	5·61	·350	1·00
Pt	31·79	·161	6·00
Cl	34·37	·968	2·1

$= (C_5 H_{13} NO)_2 (HCl)_2 Pt Cl_4$.

The filtrate separated from the phospho-molybdic acid precipitate of the base was found to contain glycerophosphoric acid. The chemolysis of lecithine therefore is complete as there were obtained—

Oleic acid - -	$= C_{18} H_{34} O_2$
Margaric acid -	$= C_{17} H_{34} O_2$ (or oxymargaric $C_{17} H_{34} O_3$?)
Glycerophosphoric acid	$C_3 H_9 P O_6$
Neurine - -	$= C_5 H_{13} N O$ (or $C_5 H_{15} N O_2$?)
Total - -	$= C_{43} H_{90} N P O_{11}$
Deduct -	$= H_6 O_3$ entered in chemolysis
Leaves -	$= C_{43} H_{84} N P O_8$ = lecithine.

The constitution of the body may be thus expressed:—

$$C_3 H_5 \begin{cases} C_{18} H_{33} O_2 \\ C_{17} H_{33} O_2 \\ OH\,(OPO)\,C_5 H_{13} NO \end{cases}$$

The formula which Strecker constructed for the lecithine he isolated from the yelks of eggs, was $C_{42} H_{84} NPO_9$ and, the body gave on chemolysis glycerophosphoric acid, cholin ($C_5 H_{15} NO_2$), oleic acid ($C_{18} H_{34} O_2$), and palmitic acid ($C_{16} H_{32} O_2$), which he, however, termed "*margaric.*" Thus great similarity in composition is exhibited between brain and egg lecithine.

Note on oleic acid.

* *Note on Oleic Acid.*—Oleic acid is generally considered to have much affinity for oxygen, so as greatly to impede attempts to obtain it in a pure state. This absorption of oxygen is considered and stated to be attended with the production of a brown colour, and a change in the nature and properties of the acid.

Pure oleic acid, prepared expressly from oil of almonds, with the view of comparing it with the oleic acid furnished by lecithine, showed none of these properties. The potash, ammonium, lead, and baryum salts were all white and showed no tendency to become coloured on exposure. The free acid was also free from this tendency and was only very faintly yellow, while its solution in ether was colourless and did not become brown on exposure. To prove the purity of the body the baryum salt was analysed for baryum and found to contain 19·73 °/₀ as against 19·60 °/₀ required by theory.

The chemistry of oleic acid and bodies nearly allied to it requires much study before such absolute and categorical statements can be made about it as those which are met with in many chemical handbooks. Many of these statements are misleading, and arise no doubt from a want of acquaintance with the subject on the part of the authors. To quote one out of a number. In Hofmann's (Prof. in Gratz) Physiological Chemistry the oleate of baryum, a diagnostic salt, is described as "shooting out in crystals" from a hot alcoholic solution. I do not believe that any chemist can obtain this salt in any other form than that of a very fine white powder, and in a great number of operations I have never obtained it in any other. I can fully confirm the description of the appearance and solubility of this salt given by Berthelot.

(4.) *Bases existing in the Brain in combination with Kephaline and Myeline.*

In the first part of these researches, New Series, No. III., 1874, p. 129, it was stated that the kephalines (and myelines) as they exist in brain matter, and as isolated therefrom, are associated with certain bases, by a power of combination derived from their acid character. These bases can only be removed and the principles obtained in a pure state by dissolving the compounds in water, and adding hydrochloric acid, which combines loosely with the principles on account of their alkaloidal character, to the exclusion of the bases, which then pass into solution as chlorides. From the kephaline hydrochlorate the hydrochloric acid can be removed by much water alone, and then on dissolving the kephaline in ether and reprecipitating it by alcohol, it is obtained pure.

In order to obtain some knowledge regarding the relative amounts and nature of the bases in combination with the phosphorised constituents of brain-matter, a quantity of solution obtained by the hydrochloric acid process, above described, and which was derived from kephaline and myeline, was submitted to analysis.

It was evaporated to dryness and the residue ignited in a previously weighed platinum dish. During this ignition much chloride of ammonium was given out, and its nature distinctly proved by condensing and analysing it.

The fused mass was dissolved in dilute hydrochloric acid, and the solution so obtained treated with excess of ammonia. The white gelatinous precipitate which was thrown down was scarcely coloured black by sulphide of ammonium. The precipitate and filtrate were submitted to qualitative and quantitative analysis.

Examination of precipitate.—The colouring matter was evidently sulphide of iron, but it did not amount to more than a trace. [The *original* solution had been subjected in a neutral state to a current of sulphuretted hydrogen with the object of removing some platinum that had been used along with the hydrochloric acid, as $PtCl_4$, in the precipitation of the kephaline and myeline from the aqueous solutions. This treatment must therefore have removed any copper and iron which were undoubtedly present.]

The precipitate was dissolved in dilute hydrochloric acid, and the calcium, magnesium, and phosphoric acid estimated as follows:—

The solution was nearly neutralised by sodic carbonate, after addition of some ferric chloride, and then an excess of pure barytic carbonate added, shaken, allowed to stand, and then filtered.

From the concentrated filtrate the baryum was removed by sulphuric acid, and the filtrate was then precipitated in the presence of

ammonia by oxalate of ammonium. The oxalate so obtained was converted by intense ignition into oxide which weighed 0·1994 grm. Ca O = 0·1423 grm. calcium.

The filtrate and washings from the calcic oxalate were treated as ordinarily in cases where it is desired to estimate magnesium, and there was obtained 0·5555 grm. $Mg_2 P_2 O_7$ = 0·1212 grm. magnesium.

The precipitate which had been produced by ferric chloride, and sodium and baryum carbonates, was dissolved in nitric acid, and the phosphorus estimated by the combined molybdate and magnesium methods. This gave 0·3266 grm. phosphorus = 0·7480 grm. phosphoric acid ($P_2 O_5$).

Examination of filtrate.—This was proved to be free from magnesium and calcium. The potassium contained in it was estimated in the usual way by means of platinic chloride, giving 11·2766 grms. of 2 K Cl, $Pt Cl_4$ salt = 3·651 grms. K Cl = 1·911 grms. potassium. The mother liquor and washings were evaporated to dryness, and the platinum was removed by extracting the ignited mass with water acidified by hydrochloric acid. The extract so obtained was evaporated to dryness and fused; the residue weighed 3·45 grms. (Na Cl) = 1·356 grm. sodium. The quantities of potassium and sodium thus found were controlled by the analysis of a separate part of the original solution containing their chlorides, and calculating from the residue obtained on evaporation, there should have been found—

A total quantity of chlorides = 7·09 grms.

There was found K Cl = 3·651 „
and Na Cl = 3·450 „

or a total of = 7·101 „

Distribution of the Bases and Phosphoric Acid.—Assuming the calcium and magnesium to have originally existed as tribasic phosphates, and any phosphoric acid remaining over to have been in combination with potassium, then we have—

Ca = 0·1423 grm. existing as 3 Ca O, $P_2 O_5$
Mg = 0·1212 „ „ 3 Mg O, $P_2 O_5$
K = 0·5663 „ „ 3 K_2 O, $P_2 O_5$
K = 1·3447 „ „ } combined directly with kephaline and myeline.
Na = 1·356 „ „ }
P = 0·3266 „ „ $P_2 O_5$ (0·748 grm.) and distributed between the Ca, Mg, and K.

It has been proved in the first research (l. c. p. 130) that kephaline was partly in combination with calcic oxyde, or lime, uncombined with any other acid. In the present research we find that there may be in kephaline (and myeline) even a much greater quantity of potash and soda in direct combination than of lime. Both observations supplement each other, the first one being qualitative only, the present research stating the quantities of the bases relatively to each other.

II.—CONTINUATION OF THE STUDY OF THE NITROGENISED PRINCIPLES.

1.—Introduction.

In the first Report of Researches on the Chemical Constitution of the Brain (New Series, No. III., 1874, p. 182 *et seq.*) I have shown that the nitrogenised ingredient peculiar to the brain, free from phosphorus and sulphur, formerly termed cerebrine, actually consisted of at least three bodies, or perhaps groups of bodies, the cerebrines, phrenosines, and kerasines, of each of which one representative had been isolated and analysed, namely, cerebrine $C_{34}\,H_{66}\,N_2\,O_8$, phrenosine, $C_{34}\,H_{67}\,N\,O_8$, and kerasine $C_{46}\,H_{91}\,N\,O_9$. The isolation was effected by fractional precipitation, partly from alcoholic solutions by cooling, partly from the same solutions by the employment of plumbic acetate.

Some of the pure substances were subjected to the influence of chemolytical agents, with a view of learning something about their chemical constitution. Thus phrenosine by being boiled with alcohol and a little sulphuric acid, was changed in a manner so as to show an increase in the carbon as compared to the nitrogen, or better it yielded up a portion of its nitrogenised nucleus. A body soluble in cold absolute alcohol was formed, perhaps the psychosine of the following research. On being boiled with water acidulated with sulphuric acid, phrenosine gave a body which reduced alkaline copper solution, among other products left unstudied. This indicated the probability of the formation of sugar, which had already been observed by Liebreich when he decomposed his protagon with hydrochloric acid. A body similar to sugar in its chemical composition was also obtained by Otto from the body termed by him cerebrine, and believed to be free from nitrogen. (See Report, 1874, p. 242.) The syrup obtained from the hydrochloric acid employed reduced cupric solution, and gave a precipitate with basic acetate of lead which turned red on heating. The analyses of the syrup gave 41·7 °/₀ C, and 7·32 °/₀ H, but did not lead the author to identify his product with sugar, which contains 40 °/₀ C, and 6·6 °/₀ H.

I next observed that when phrenosine was heated by itself to about 160° it fused, became dark, and evolved water with ebullition, just as sugar does when it passes into caramel. This phenomenon supported the surmise of the presence in these bodies of a radical closely related to and capable of transformation into sugar. The striking affinity of the nitrogenised principles for water, by means of which they swell in hot water like starch on being boiled, seemed also to point in a similar direction, namely, to the presence of a starch radicle which might determine this swelling capacity; but as the phosphorised matters had a similar though less pointed property, and were known not to yield any sugar on chemolysis, this property was not considered as an important guide to the inquiry.

As sugar had been obtained from so-called protagon, which is now admitted to have been a mixture of several phosphorised with several nitrogenised principles, and from a matter free from phosphorus, and supposed to be free from nitrogen, but in which the nitrogen had probably been overlooked, I judged that the experiment might be repeated with even better chance of success upon those mixtures of cerebrine and phrenosine, which are obtained in the form of the earlier precipitates in the course of the fractional precipitations employed for

isolating the pure principles. And I further hoped that the chemolysis of these cerebrine bodies, which had no very marked basic or acid properties, and showed an indifference towards acids and bases similar to that shown by so-called nitriles or imides, might produce simpler radicles of more decided combining propensities, being either acids or alkaloids, and therefore easier to seize and study. I also hoped that, as in the case of the phosphorised substances, one or more radicles might be found to be common to all the cerebrine bodies, and be the cause or causes of the identity of the reactions, which like the purple with sulphuric acid and sugar, they all uniformly exhibit. And I expected that if these simpler products could be obtained in quantity from these mixed materials, they might help to find means for a complete separation of all the matters and for the formation of their structure formulæ, in the same manner as the chemolysis of the mixed phosphorised bodies has led to the discovery of their fundamental and uniform radicles, and has thereby greatly aided the elucidation of their differences.

These expectations have been to a large extent fulfilled, although the researches are not yet by any means completed. Five classes at least of bodies have been obtained from cerebrine and phrenosine by chemolysis, both with acids and alkalies. Of these one, *sugar*, already previously known, has now been determined as actually formed by chemical reactions not only, but by optical test and quantitative analysis. A second body, an alkaloid, *psychosine*, is new to chemical science, and for the first time described in this research. *Three new acids*, forming baryum salts, some containing nitrogen, some free from it, await further study. Other matters isolated may be intermediate products; others, again, products of the secondary chemolysis of the five bodies isolated and identified. Among the latter is a *volatile alkali*, obtained under circumstances which do not yield psychosine, and an *amorphous acid* soluble in water, obtained when sugar is not obtained, because the chemolytic acid probably transforms both psychosine and sugar into simpler products when its influence is continued longer or becomes more energetic with the aid of higher temperature and pressure. For effecting chemolysis sulphuric acid on the one, and baryta hydrate on the other, were alone employed, as being those reagents which can be most easily and completely removed from the new products.

2.—Chemolysis of Cerebrine and Phrenosine by Baryta.

(*a.*) *Attempt to isolate the Nitrogen Nuclei in Cerebrine and Phrenosine.—Series I.*

Experiment I.—The preparation selected for this experiment was "prep. 1314," being the first hour's deposit from first hour's cerebrine from ox W.M. On examination it was found to contain a small proportion of phosphorus (in all probability as myeline). When freed from this the body may be considered as a mixture of one molecule of cerebrine with two molecules of phrenosine, since on analysis it yielded the formula $C_{48}\ H_{94}\ N_2\ O_9$ (*see* Report, New Series, No. III., 1874, p. 185).

40 grammes of this preparation, together with 80 grammes $Ba\,H_2\,O_2$ and sufficient water to form a paste were enclosed in glass tubes, which were then hermetically sealed and heated to 135° for several hours, after which the tubes were broken and their contents removed, the solid matter separated by filtration and washed with water until free from excess of $Ba\,H_2\,O_2$. The portion insoluble in water was in this

experiment at once decomposed by means of H Cl in presence of ether and water, the ether extract distilled to dryness; the residue so obtained dissolved in water containing NH_3, and this solution heated with $BaCl_2$ in excess. The reconstituted baryum salts thus obtained were next extracted with alcohol and ether till each of these solvents ceased to take up any further quantities.

The alcohol and ether extracts were proved to contain baryum salts of fatty acids in small quantity, and the final insoluble larger quantity of matter after extraction with alcohol and ether was shown to be a baryum salt of an amidated fatty acid. The analysis of this latter and other salts are withheld until such time when the connexion between them and their relation to the original molecule are more evident.

The aqueous solution was proved to contain matters of a basic character in small quantity, and these were studied, as far as material would permit, with regard to their behaviour to such reagents as phospho-molybdic acid, &c.

The results of this pioneering experiment may be stated to be as follows:—The body under examination yielded when chemolysed with $Ba H_2 O_2$ in sealed tubes for several hours at 135°, some unchanged cerebrine, a base or bases soluble in water, small quantities of baryum salts soluble (1) in alcohol, (2) in ether, (3) in alcohol and ether, and finally a considerable quantity of an insoluble baryum salt of an amidated fatty acid.

Experiment II.—The preparation used was that described under Experiment I., but the mode of procedure observed somewhat different, viz., the temperature of the sealed tubes was not kept constant at 135°, but allowed to fall as low as 100° during the operation, and the heating was continued for a less period of time.

50 grammes of the preparation, together with 100 grammes $Ba H_2 O_2$ and 50c.c. of water were employed. After removal of the contents of the tubes and washing of the solid matter free from excess of $Ba H_2 O_2$, the portion insoluble in water was at once extracted with alcohol of 85 %, and finally with ether. All products appeared in the first instance similar to those of the first experiment, but on a final evaporation of the concentrated alcoholic mother-liquors from the several extractions, after these had been allowed to deposit on cooling, a residue was obtained varying markedly in character from the parallel product of the previous experiment.

On examination of this body it was found to be insoluble in water, but completely dissolved on addition of a few drops of H Cl. In this solution phospho-molybdic acid produced a yellow precipitate of a colloid nature, platinum tetra-chloride a copious precipitate of a similar nature soluble in absolute alcohol.

Ammonia gave a voluminous white precipitate (shown afterwards to be the free body), soluble in absolute alcohol, which solution on evaporation yielded a transparent crystalline mass of microscopic needles and plates.

Discovery of a new alkaloid, Psychosine.

Here, then, was a body of a distinctly basic character, crystalline in structure, insoluble in water, but yielding a soluble hydrochlorate, and possessing further properties indicating its definite and homogeneous character.

Purification.—The whole available quantity was dissolved in water containing HCl, the solution filtered from some insoluble matter and phospho-molybdic acid in HNO_3 solution added in excess. The precipitate so obtained was, after trituration with water thrown on a filter, and after freeing from excess of HNO_3 decomposed by $Ba H_2 O_2$ in the usual

way, excess of $Ba H_2O_2$ being removed by means of CO_2. From the solid matter the new base was obtained by extraction with absolute alcohol, the alcoholic solution evaporated to dryness, and the residue so obtained placed over H_2SO_4 in vacuo. After some days it admitted of pulverisation, and after drying finally at 100° the following preliminary analysis was made.

The formula deducible from this analysis is stated with all the reserve necessarily accompanying the determination of the formula of a body of very difficult properties and not yet sufficiently investigated.

Preliminary analysis:—Substance dried first in vacuo over H_2SO_4, finally at 100°.

(*a*) 0·3114 grm. burned with lead chromate and copper (free from occluded hydrogen) gave 0·7064 grm. CO_2 and 0·2830 H_2O = 61·86 % and 10·09 % H.

(*b*) 0·0234 grm. gave by combustion in vacuo with cupric oxide and copper 0·54 c.c. nitrogen gas normal = 2·88 % N.

Computation of analyses.

Per-centage found.	÷ At. Wgts.	÷ N=1
C=61·86	5·155	25·1
H=10·09	10·097	49·2
N= 2·88	0·205	1·0
O=25·17	1·573	7·6

$= C_{25} H_{49} N O_8$.

To this body I have given the name of *Psychosine*.

Properties of Psychosine and its Hydrochlorate.

The free base.

1. Crystalline as deposited from its alcoholic solution.
2. Insoluble in water. The crystalline body when covered with water swells up but does not dissolve. Alkaline reaction.
3. Soluble in very dilute HCl to a brilliantly clear solution, soluble in alcohol and in ether.
4. Soluble in dilute H_2SO_4.
5. With H_2SO_4 and sugar gives the *purple reaction* peculiar to the cerebrine and biliary bodies.
6. In its alcoholic solution $Ba H_2O_2$ causes a gelatinous precipitate.
7. On heating on platinum foil burns easily with a luminous flame, swelling up and leaving much carbon.

The Hydrochlorate.

1. Soluble in water. The base is possibly diacidic, as its solution maintains an alkaline reaction in presence of a minimum of HCl necessary for its solution.
2. HNO_3 produces in the solution a transparent gelatinous precipitate soluble on further addition of water, again precipitated by further addition of HNO_3, and so on until HNO_3 ceases to give a further precipitate in the diluted solution.
3. The precipitate by HNO_3 is entirely soluble in ether.
4. Phospho-molybdic acid produces in the solution a copious yellow adhesive precipitate, becoming granular on trituration with large excess of the reagent. This precipitate is soluble in ether, with a brilliant yellow colour. It is necessary to avoid all excess of concentrated nitric acid in this reaction, as the base is easily nitrited and thereby changed in fundamental properties.

5. With platinum tetrachloride an amorphous yellow precipitate soluble in alcohol, precipitated from its alcoholic solution by ether, easily soluble in large excess of ether.
6. With $Au Cl_3$ and HCl a yellow precipitate.
7. With $Cd Cl_2$ a white amorphous precipitate.
8. With picric acid a yellow amorphous precipitate; with tannic acid no precipitate; with ammonia a dense white precipitate (free body) soluble in alcohol, thence deposited crystalline.

The hydrochlorate further gave with KHO precipitate; NaHO precipitate; $Ba H_2 O_2$ dense precipitate; $Na_2 CO_3$ pulverulent precipitate, probably carbonate; $Hg Cl_2$ in excess of KI, dense white precipitate with a solution of chloride of bismuth in excess of IK, a yellow precipitate, easily soluble in alcohol.

b. Second Series of Experiments.

In considering the broad results of the above first series of experiments, and by the light of Exp. II., it was determined to institute a new series of experiments, in order to fix the governing conditions under which the new base might be isolated, and at the same time to look for this body in various other preparations belonging to the cerebrine group. The six following experiments were undertaken, the last three being attended with success, psychosine being isolated in considerable quantity.

A special tube was employed in the first five experiments. This was a strong brass tube closed at one end, 18 inches long and $1\frac{1}{2}$ inch diameter, thickly lined with platinum, the open end being closed by means of a solid platinum cap and lever screw. The tube when charged was heated in the air-bath to the required temperature.

The following preparations were used:—In the first four experiments "prep. 1317," being first hour's deposit from second hour's cerebrine; in the fifth experiment "prep. 1315," being second hour's deposit from first hour's cerebrine; in Exp. VI., "prep. 1316," being third hour's deposit from first hour's cerebrine.

Experiments I.–III. Series II.—45 grms. "prep. 1317," 100 grms. $Ba H_2O_2$, and sufficient water to form a paste, were heated in the platinum tube above described, for from 16 to 18 hours at 135°.

No psychosine was isolated in these experiments, all products being parallel to those of Exp. I. Series I.

Experiment IV. Series II.—45 grms. "prep. 1317," 100 grms. $Ba H_2O_2$ and 100 c.c. water were heated in the platinum tube for three hours at 100°.

Much psychosine was obtained from the concentrated alcoholic mother liquors (*see* Exp. II. Series I.)

Experiment V. Series II.—45 grms. "prep. 1315," together with 100 grms. $Ba H_2O_2$ and 100c.c. water, were heated in the platinum tube for $3\frac{1}{2}$ hours at 100°

More psychosine was here isolated than in any previous experiment, the final alcoholic mother liquors yielding on evaporation a transparent highly crystalline almost colourless mass.

Experiment VI. Series II.—25 grms. of "prep. 1316," together with 50 grams. $Ba H_2O_2$ and sufficient water, were boiled for five hours in a platinum dish, the loss of water by evaporation being from time to time replenished and the whole constantly stirred. Here also a not inconsiderable quantity of the new body was isolated.

In all these chemolyses an aqueous solution was obtained in which the presence of sugar was distinctly indicated. This product of decomposition, though present in such small quantity, is of great importance when considered in conjunction with the results obtained in those series of experiments in which H_2SO_4 was used as a chemolytic agent.

In those experiments psychosine and sugar were among the main products of decomposition. Further similarity of results becomes evident in comparing these methods of chemolysis, but it is for future research to establish their absolute parallelism. As regards the chemolyses with baryta, it is evident that at 100° in sealed tubes, or even by simple boiling in an open vessel, these cerebrine bodies yield as one product of decomposition a new base; but at 135° in sealed tubes no new base is isolated. The conclusion is obvious that this body is an intermediate product of decomposition, and is further decomposed on further heating. The particular products of its ultimate decomposition will be matter for future research.

It is likewise for further research to substantiate or annul the hypothesis that psychosine is a nucleus common to the molecules of cerebrine, phrenosine, and perhaps kerasine.

3.—Chemolysis of Cerebrine and Phrenosine by Sulphuric Acid.

Experiment I.—The preparation used in this experiment was analysed with the following results :—

(*a.*) 0·290 grm. substance gave 0·7200 grm. CO_2 and 0·296 grm. H_2O = to 67·710 °/₀ C and 11·344 °/₀ H.

(*b.*) 0·3500 grm. gave 9·4c.c. N normal = 3·359 °/₀ N.

Computation of analyses.

	Per-centages.	÷ At. Wgts.	÷ N = 1.	
C	= 67·710	5·642	23·6	× 2
H	= 11·344	11·344	47·4	× 2
N	= 3·359	·239	1·0	× 2
O	= 17·589	1·099	4·5	× 2

$= C_{48} H_{94} N_2 O_9.$

The body was therefore probably a mixture of one molecule of cerebrine with two molecules of phrenosine, very similar to the one described on p. 185 of Rep. 1874.

10 grms. of this preparation were boiled in 100 c.c. of water, containing 4 grms. H_2SO_4 during two hours. At first the whole mixture grew thick like starch paste; it next cleared and separated into a fluid and a granular white matter which was soft in the hot state. Where the dish became at all dry at the sides a purple colour appeared. The filtrate and solid matter were examined as under.

Examination of sulphuric acid solution.

The sulphuric acid was removed by baryta, and the excess of the latter by carbonic anhydride. The concentrated filtrate had a smell which reminded of hot sugar solutions. Portions were examined as follows :—

(1.) A little evaporated to dryness left a yellow residue which fused and burnt like sugar.

(2.) Not distinctly sweet to the taste.

(3.) Contained baryta in combination (sugars have this property).

(4.) With cerebrine and sulphuric acid it gave the purple reaction strongly and at once.

(5.) It reduced in a normal manner cupric sulphate as applied in Fehling's solution.
(6.) With iodine it gave a strongly brown colour.
(7.) Absolute alcohol precipitated it as a viscid mass which became hard on contact with fresh alcohol, the alcohol dissolved a small quantity.
(8.) On boiling with basic lead acetate the precipitate turned pink; acetate of lead and ammonia gave a precipitate which behaved similarly.

The substance was therefore probably sugar.

Examination of solid matter.

It was not examined at all in the state in which it was left by the sulphuric acid, but was boiled with baryta water for several hours. This gave a solution containing a mere vestige of a body having the characters of a base.

The baryum salts were dried and extracted with boiling nearly absolute alcohol. The extracts deposited a baryum salt of an organic acid, which was too small in quantity for further examination.

The alcoholic solution was evaporated to dryness on a water bath, and left a fluid yellowish mass which set on cooling into a soft solid. It had the properties of *psychosine.*

With hydrochloric acid and water it gave a starch-like solution, becoming clear on heating, and setting like jelly on cooling again. With more water a clear filterable solution was obtained which gave the following reactions:—

(1.) With nitric acid, a white curdy precipitate which was soluble in more water and nitric acid, and which was also soluble entirely in ether.
(2.) The nitric acid solution obtained in (1) gave a bulky and adhesive phospho-molybdic acid precipitate which was also entirely soluble in ether.
(3.) With platinic chloride it gave a bulky precipitate entirely soluble in alcohol.
(4.) No reducing action on alkaline cupric sulphate.

The Baryum Salts insoluble in alcohol were decomposed with hydrochloric acid in the presence of ether. This gave an ether solution containing a swollen matter in suspension; it was distilled to dryness, and after attempting several proceedings which were rendered futile by the insoluble matter alluded to, the residue was recrystallised from alcohol. The solution on cooling threw down a bulky white deposit; the mother liquor was discarded. The deposit was dried, and again recrystallised from watery alcohol. The final product fused about 70° C., and contained nitrogen, as proved by heating it with soda lime, when a volatile ammonium body was evolved in quantity and an oily body sublimed; this latter set on cooling but gave no ammonium salt.

The product gave a strong purple reaction with sulphuric acid and sugar.

It was now also insoluble in ether and only partially dissolved on the addition of hydrochloric acid; the part therefore which is soluble in ether must be a hydrochlorate.

It has not yet been analysed.

Experiment II.— In this experiment 21 grms. of a similar preparation to that used in Experiment I. were chemolysed in the platinum tube

previously described with 150c.c. water containing 3 grms. sulphuric acid (=2 °/₀ solution), at a temperature of 130—160° C. during three hours.

Examination of Sulphuric Acid Solution.

It was neutralised while hot by means of baryum carbonate, filtered and concentrated. The solution had all the characters of the corresponding solution obtained in Experiment I., and gave also the following tests :—

(1.) Would not crystallise.
(2.) Neutral to test paper.
(3.) Soluble in dilute alcohol ; insoluble in absolute alcohol.
(4.) With ammoniacal nitrate of silver a reduction takes place on heating, and a silver mirror forms.
(5.) Produced a faint reduction of mercuric subnitrate.
(6.) Reduced a solution of trisnitrate of bismuth in sodic carbonate solution.
(7.) With pure glycocholic acid and sulphuric acid gave a brilliant Pettenkofers reaction.
(8.) With concentrated sulphuric acid, blackened.

The material which remained after the above re-actions had been made was freed from baryum in combination by means of careful precipitation with very dilute sulphuric acid. The solution was next concentrated, and then precipitated by absolute alcohol, dried at 95° C., and analysed 0·2784 grm. gave 0·3854 grm. CO_2 and 0·169 grm. H_2O, =37·75 °/₀ C, and 6·74 °/₀ H.

Computation of analyses.

Per-centages.	÷ At. Wgts.	÷ C=6.
C=37·75	3·146	6·
H= 6.74	6·74	12·6
O=55·51	3·469	6·6
	$=C_6H_{12}O_6$	

The carbon is rather low, as some difficulty was experienced in the burning. The analysis and reactions together, however, leave no doubt that the product was sugar. This was further confirmed by examining a solution of the body after decolorisation by charcoal, optically.

A solution containing, as determined by copper reduction method, 2·74 °/₀ of the sugar, was found to turn the plane of yellow sodium light 4° 24′ to the right at a temperature of 79° F. in a tube 200 m.m. long.

Examination of the Solid Product.

Washed and placed in ether, it chiefly dissolved, but left insoluble a gelatinous matter to be described further on.

The ether extract was distilled and the residue carefully examined for psychosine, but none was present.

After this it was recrystallised twice from 85 °/₀ alcohol, containing animal charcoal (which removed the colour), and the deposited matter was isolated and preserved for analysis. It was at this stage insoluble in ether, but soluble in the presence of HCl, and contained nitrogen ; it fused at 70° C. The alcoholic mother liquor contained what seemed to be free fatty acid, soluble in ether. It furnished a baryum salt. *The gelatinous matter* was dissolved in hot absolute alcohol ; it only deposited a trace of matter on cooling. The alcoholic solution was evaporated to

dryness on a water bath, and taken up in water and hydrochloric acid, in which it dissolved to a gelatinous paste which became quite clear when hot. This solution gave—

(1.) A bulky characteristic precipitate with phospho-molybdic acid.
(2.) A characteristic precipitate with watery platinic chloride ; this precipitate was soluble in alcohol.
(3.) A precipitate with ammonia.
(4.) A precipitate with picric acid.

The matter was therefore psychosine, but after these tests and others had been made, there was not left enough for analysis.

The products of the chemolysis of cerebrine and phrenosine, with sulphuric acid, are therefore sugar, psychosine, a body fusible at 70° C. and containing nitrogen (perhaps an amidated fatty acid), a fatty acid free from nitrogen and which gives a baryum salt. The gelatinous body which accompanied the amidated body in Experiment I., and rendered the ether solution unfilterable, is perhaps to be considered as identical in nature with that dissolved in the ether ; this is plausible because in the absence of hydrochloric acid both were insoluble in ether.

That body in Experiment II. which was at one time soluble in ether (as sulphate ?), also became ultimately insoluble in ether, and inasmuch as it had the same fusing point as the similar one in Experiment I. it may be considered as allied to it or identical with it.

It is probable that the small quantity of fatty acid which was obtained was derived from the amidated body by the chemolysis having proceeded further towards ultimate results. The chemolyses effected by baryta gave results similar to those described above ; while psychosine formed the most prominent product the evidence that sugar was formed was also indisputable. An insoluble in ether baryum salt was also obtained which with ether and hydrochloric acid behaved like similar preparations described in the sulphuric acid chemolyses ; and from the fact that this contained nitrogen, the free body may be regarded as identical with the one described above which fused at 70° C., and also contained nitrogen.

The fatty acid, whose baryum salt was obtained and found to be soluble in ether, was perhaps identical with the fatty acid which remained in small quantity in the alcoholic mother liquor of the recrystallised amidated substance obtained in Experiment II. with sulphuric acid.

It is therefore evident that the bodies of the cerebrine class show some analogy to the class of bodies known in chemistry as saccharides or glucosides, which are derived from one or several molecules of any sugar, by the substitution of one or several hydroxyls by one or several molecules of acid. Thus distearic glucoside, $C_{42} H_{78} O_7$ is produced according to the equation $C_6 H_{12} O_6 + 2C_{18} H_{36} O_2 = C_{42} H_{78} O_7 + 3H_2 O$. These glucosides yield the original substances from which they are derived by being boiled with dilute acids. But the cerebrines differ from the saccharides as yet extracted from natural products or obtained by chemical synthesis in this, that they contain nitrogen either in the form of amidated fatty acids, or of ammonium bases, or both. Moreover at least one of the fatty acids as yet met with in cerebrine seems to be peculiar and as yet unknown. The foregoing research has therefore had to contend with difficulties which are too well recognised in animal chemistry to require further discussion. But it has also furnished important data towards the elucidation of the question proposed, and fixed the direction in which inquiry will have to be continued.

* *Note on the purple reaction of the bodies of the cerebrine group and certain fatty acids with sulphuric acid and sugar.*

All the bodies of the cerebrine group, and certain decomposition products of kephaline, myeline, cerebrine, and phrenosine, give with strong sulphuric acid and sugar that colour reaction which as applied to biliary substances is known under the name of Pettenkofer's test.

Psychosine from cerebrine; the amidated fatty acid from cerebrine; the fatty acid from kephaline, which yields a baryum salt soluble in ether; and an acid from myeline—all these give the purple colour test.

Now cerebrine gives with sulphuric acid alone, and without the addition of sugar, this purple colour, but a longer time is required for its development than when sugar is also used.

The sulphuric acid may be supposed to act by splitting up the molecule of cerebrine into fatty acids (amidated or otherwise) on the one and a simple saccharide on the other hand, so that the addition of sugar at this stage at once developes the purple colour; but if sugar be not added, the sulphuric acid after more prolonged influence splits up the residue of the molecule of cerebrine, i.e. the simple saccharide, into a fatty radicle and sugar, and thus furnishes the essential ingredients for the purple reaction.

Ordinary mercantile palmitic acid fails to give it; on the other hand, mercantile stearic acid, and oleic acid from oil of almonds and from lecithine, do give the reaction.

III.—STUDY OF THE PRINCIPLES SOLUBLE IN WATER.

1.—Water Extracts of Oxbrains.

Experiment I.—The concentrated water extracts of brains employed in the following processes had a gravity of 17° B = 1·13 sp. gr.

The solution was treated with baryta water to complete precipitation (*a*), the filtrate was completely precipitated with neutral acetate of lead (*b*), and the filtrate from this precipitate was completely precipitated by basic lead acetate (*c*). The mother-liquor was reserved (*d*).

(*a.*) *Examination of Baryta Precipitate.*—It was washed and dried, and found to contain 77·8 % ash. It was now divided into two halves, which were treated as described below.

Treatment of Baryta Precipitate with H Cl.—This gave a red solution and a precipitate chiefly consisting of $BaSO_4$. This precipitate was digested in warm dilute caustic potash; the filtrate gave with H Cl an amorphous precipitate, so also with acetic acid. The whole was now treated with acetic acid and the precipitate redissolved in caustic potash, and re-precipitated by acetic acid; the product appeared to belong to the uric acid group, but was proved not to be uric acid itself.

Treatment of Baryta Precipitate with Na_2CO_3.—On digestion there was obtained a solution which contained matter precipitable by acetic acid, and of the same nature as that from the H Cl extract.

(*b.*) *Examination of the normal Lead Precipitate.*—Washed and found to give 67 % of residue on ignition of a portion. This residue consisted of lead, its oxide, and much chloride.

It was now suspended in water and decomposed by sulphuretted hydrogen. The filtrate was now precipitated by phospho-molybdic acid, and the precipitate washed first with water acidified with nitric acid, and then with 85 % alcohol. On decomposing the precipitate with baryta in the

ordinary way, there was obtained a solution which contained alkaloidal matter, as evidenced by the precipitates it gave with $HgCl_2$, $AuCl_3$, and picric acid.

The mother liquor from the phospho-molybdic acid precipitate was also passed through the baryta process, and the excess of baryta removed by CO_2; this gave a colourless filtrate which produced with Fe_2Cl_6 a yellowish white precipitate. The filtrate from this gave a further precipitate on boiling. They were united dissolved in ammonia, the iron removed by NH_4HS, and the filtrate concentrated, when it crystallised.

(*c.*) *Examination of the Basic Lead Precipitate.*—Washed, then decomposed by H_2S in water. The filtrate was concentrated and a small amount of alcohol added, which caused a large crop of crystals to be deposited on cooling; a further quantity was obtained from the mother liquor on continued concentration. These crystals were of pure inosite; they were sweet to the taste and were further identified.

The alcoholic mother liquor from the last crop of inosite proved to contain alkaloidal matter precipitable by $HgCl_2$. It was extracted by means of the phospho-molybdic acid process.

(*d.*) *Examination of Mother-liquor.* This was concentrated to a syrup and was tested for urea, the presence of which in any quantity above a trace was disproved. The solution was now divided into halves, which were separately examined.

(*a.*) Was precipitated to completion by $HgCl_2$, and the precipitate after washing decomposed by SH_2; on concentration of the filtrate in vacuo over sulphuric acid, crystals were obtained (=Alkaloid No. I.). The mother-liquor gave with absolute alcohol a copious precipitate, which appeared on further examination to consist of a second alkaloid in combination as hydrochlorate; in the presence of free acid it was soluble in alcohol.

Alkaloid No. I. as hydrochlorate in solution gave the following reactions:—

(1.) With $AuCl_3$ a bulky yellow precipitate.
(2.) With $PtCl_4$ no precipitate; addition of alcohol produced one on standing.
(3.) I in KI, bulky adhesive precipitate.
(4.) $HgCl_2$ in KI, precipitate.
(5.) Picric acid, a precipitate.

It was observed that evaporation of the alkaloid in presence of HCl to dryness gave a residue which when redissolved in water gave a bulky precipitate with $PtCl_4$.

The free base in water obtained by decomposition of the hydrochlorate with MgO gave in that state no $PtCl_4$ precipitate, but was precipitated by $HgCl_2$. The crystallised base was recognised as *hypoxanthine.*

(*b.*) The other half was freed from lead and baryta by sulphuric acid and the resulting solution again concentrated, after which it was freed from lactic acid as far as possible by extraction with large and repeated volumes of ether; from the watery solution the alkaloids were now obtained by application of the phospho-molybdic acid process. These were transformed into hydrochlorate, and on concentration a crop of crystals were obtained (Hypoxanthine + HCl). The substances obtained, therefore, in this experiment were:—

(1.) A matter resembling but not identical with uric acid.
(2.) A crystallisable acid giving a ferric salt.
(3.) Inosite.
(4.) Hypoxanthine and another base.
(5.) Lactic acid.

Experiment II.—In this experiment the solution was perfectly extracted by ether (*a*) in the presence of sulphuric acid, an operation which extended over some months. Meanwhile crystals (*b*) formed gradually in the solution; these were separated from time to time and collected. Ultimately the watery solution was passed through the phospho-molybdic acid process (*c*), the mother liquor resulting from this precipitation being reserved (*d*).

(*a.*) *Examination of Ether Extracts.*—These were distilled till free from ether, and the resulting yellow solution, which was strongly acid, was boiled with oxide and carbonate of zinc, filtered and evaporated. In this way a considerable quantity of zinc salt has been accumulated and awaits further investigation; it is probably lactate of zinc.

(*b.*) *Examination of Crystalline deposit.* — These crystals were washed with water and dissolved in caustic potash, then reprecipitated in a crystalline form by sulphuric acid, subsequently they were recrystallised several times from water. They had the following characters:—

(1.) Difficultly soluble in water.
(2.) Free from sulphuric and hydrochloric acids.
(3.) On ignition decrepitate, blacken, scintillate, and leave a fusible residue which is dissipated in white fumes on further heating.
(4.) From a solution of the crystals in potash dilute sulphuric acid precipitated a highly crystalline substance.
(5.) Alcohol also produces a precipitate in the potash solution.

A watery solution gave the following tests:—

(6.) With $Pt Cl_4$ no precipitate, but a bulky one on the addition of alcohol.
(7.) $Ca Cl_2 + N H_3$ gave a copious precipitate, readily soluble in nitric acid.
(8.) $Ba H_2 O_2$ a copious precipitate, soluble in $H N O_3$.
(9.) $Mg S O_4 + N H_4 H O$, precipitate.
(10.) $Fe_2 Cl_6$ no precipitate.
(11.) $Pb (C_2 H_3 O_2)_2$ a copious precipitate insoluble in water at 100°, soluble in nitric acid.

The whole quantity was now dissolved in water, precipitated by lead acetate and decomposed by $S H_2$; the concentrated filtrate had an acid reaction and crystallised on cooling; a portion of the product was dissolved in water, neutralised by $Na H O$, and the solution tested gave—

(12.) A good silver salt with $Ag N O_3$, soluble in $H N O_3$.
(13.) Did not prevent the precipitation of $Fe_2 Cl_6$ by $N H_4 H O$.
(14.) Gave no precipitate with $K_2 S O_4$ on stirring.

These tests exclude tartaric acid, while the exact nature of the acid has yet to be determined.

(*c.*) *Examination of Phospho-molybdic Acid precipitate.* — The solution resulting from the decomposition of this precipitate by baryta, and freed from excess of baryum by $C O_2$, was treated with excess of oxide of silver. After several hours digestion in the cold, filtered and precipitated by $Ag N O_3$. The precipitate so obtained was decomposed by $S H_2$ and the resulting solution, which was strongly acid, gave the following reactions:—

(1.) With $Ag N O_3$ a precipitate which was greatly increased in amount by neutralising the solution.
(2.) This silver salt was entirely soluble in excess of $N H_3$ or $H N O_3$.

The silver oxide precipitate was also decomposed by SH_2, and the solution thus obtained was found to contain some of the same matter as that whose properties have just been described.

(*d.*) *Examination of Mother-liquor after Phospho-molybdic acid precipitate.*—This was completely precipitated by BaH_2O_2 in the hot and the filtrate freed from excess of baryum by CO_2. The filtrate was allowed to cool and then completely precipitated by $HgCl_2$; after precipitation with $HgCl_2$ the filtrate was reserved (*e*); the precipitate after washing with water was decomposed by H_2S. This gave a dark-red solution of a broth-like odour; this was treated with excess of Ag_2O when NH_3 was evolved. After two or three hours digestion HNO_3 was added to cause the precipitation of AgCl that might otherwise have been dissolved by the NH_3; filtered and filtrate kept. On extraction of the silver precipitate with dilute HNO_3 in the hot much dissolved, and was deposited on cooling in white silky masses of hypoxanthine silver nitrate salt, which was purified by decomposition with H_2S, thus giving free hypoxanthine nitrate.

The filtrate from the Ag_2O precipitate was rendered ammoniacal and nitrate of silver added; this gave no precipitate until the addition of HNO_3, which caused a deposit; this deposit was soluble in boiling water, and the solution had the following characters :—

(1.) With $AgNO_3$ a feeble precipitate.

(2.) With ammoniacal nitrate of silver a bulky precipitate soluble in excess of ammonia or nitric acid.

(*e.*) *Treatment of Mother liquor from $HgCl_2$ precipitate.*—This was concentrated and completely precipitated by basic acetate of lead, which precipitate on decomposition with SH_2 gave a solution which yielded inosite on evaporation, and a mother liquor from which strong alcohol separated an oily precipitate which crystallised on cooling, and which was regarded as a derivative of inosite.

The following bodies, therefore, represent the results of the foregoing study :—

Hypoxanthine, and a second base.
New crystallisable acid giving no insoluble iron salt.
Lactic acid.
Inosite, and what is perhaps a product of change of inosite.

Experiment III. — A quantity was passed through the phospho-molybdic acid process, and the product was treated with excess of oxide of silver filtered and washed.

Treatment of Precipitate.—Decomposed by SH_2, filtered, and the sulphide of silver extracted with much boiling water, the filtrate and water extracts were united and evaporated to dryness, and thus furnished a residue of hypoxanthine with some little foreign matter; the hypoxanthine was purified by dissolving in a little HNO_3, decolorising with charcoal, and re-precipitation with NH_3.

Treatment of the Filtrate.—This was rendered ammoniacal and precipitated by ammonio-silver nitrate, washed with water containing a little ammonia, then decomposed by SH_2; the yellow filtrate made a deposit on concentration and gave a yellow mother-liquor.

Examination of Deposit.—This was dissolved in boiling water, and was re-precipitated on cooling. It had the following characters :—

(1.) Its aqueous solution gave with $AgNO_3$ a white gelatinous precipitate insoluble in excess of ammonia, but entirely soluble in much water and nitric acid, from which solution it deposited on cooling in a perfectly white form.

These tests would seem to indicate that the body under examination was hypoxanthine, although the two next tests appear to exclude both hypoxanthine and xanthine.

(2.) Warmed with HNO_3 and gently dried it left a yellow residue which did not change colour on heating, but burnt and evolved cyanogen, leaving a charcoal.

(3.) The yellow body failed to give the purple coloration with KHO.

In all probability, therefore, this body was a new member of the xanthine series.

On examination of Yellow Mother-liquor, it was found to contain hypoxanthine as characterised by its silver nitrate compound, &c.

In this investigation, therefore, besides hypoxanthine, a substance of very similar properties, and apparently identical with a similar body existing in diabetic urine, was found.

General note regarding the isolation and separation of the Alkaloids contained in Ox Brain.

The presence of the alkaloids in the water extracts of brain matter is indicated by the precipitates which they give with $AuCl_3$, I in KI, $HgCl_2$ in KI, picric, tannic, and phospho-molybdic acids.

They may be obtained as shown in the preceding pages by the application of the phospho-molybdic acid process, $HgCl_2$ process, and collaterally by the basic lead acetate process (for inosite). The latter process, however, does not yield them if preceded by the phospho-molybdic acid process. They may be separated when in the free state by evaporation to a syrupy consistency when the hypoxanthine is deposited while the second base is uncrystallisable. The same remarks apply to a mixture of the hydrochlorates, the hypoxanthine compound in this case being obtained in a crystalline form. Neither the watery solution of the free hypoxanthine nor of its hydrochlorate gives a $PtCl_4$ precipitate. The hypoxanthine may be purified by dissolving in boiling water and addition of excess of silver nitrate and nitric acid. The precipitate so formed gradually dissolves in hot nitric acid, and from the filtered solution deposits on cooling in a mass of homogeneous needles. Obtained in this way it is pure, as testified by the following analysis :—

(*a.*) 0·5628 grm. gave 0·255 grm. Ag Cl = 34·100 °/₀ Ag.

(*b.*) 0·4834 grm. gave 0·350 grm. CO_2 and 0·067 grm. H_2O = 19·746 °/₀ C and 1·539 °/₀ H.

(*c.*) 0·4756 grm. gave 89·46c.c. nitrogen normal = 23·516 °/₀ nitrogen.

Computation of analyses :—

Per-centages found.	÷ At. Wgts.	÷ Ag = 1.
C = 19·746	1·645	5·2
H = 1·539	1·539	4·8
N = 23·516	1·679	5·3
O = 21·099	1·318	4·1
Ag = 34·100	0·315	1·0

$= C_5H_4N_4O + AgNO_3$.

A combination of the hypoxanthine with silver was also obtained by precipitation of its solution with ammoniacal silver nitrate; it contained 60·46 °/₀ silver, whereas had it been pure $C_5H_4N_4OAg_2$, it should have contained 61·7 °/₀.

The hydrochlorate of the second base is soluble in alcohol but precipitated by ether; on the whole it is a perishable compound. In one

experiment where the hypoxanthine had been removed from a mixture of the two bodies, this second base was again passed through the phospho-molybdic process, the product gave a precipitate with Ag N O_3 in the presence of H N O_3, which proved to be a further quantity of hypoxanthine salt. Thus purified the second base was again passed through the phospho-molybdic acid process, then converted into gold chloride salt and analysed.

(*a.*) 0·5944 grm. gave 0·1894 grm. gold=31·864 °/₀ gold.

(*b.*) 0·530 grm. gave 0·243 grm. Ag Cl=11·34 °/₀ chlorine.

(*c.*) 0·5570 grm. gave 0·559 grm. CO_2 and 0·187 grm. H_2O = 27·37 °/₀ C and 3·71 °/₀ H.

(*d.*) 0·3612 grm. gave 34·3c.c. nitrogen normal = 11·88 °/₀ N.

Computation of analyses.—In this compound the gold stands to the chlorine as 1:2; deducting now the gold and chlorine and recalculating the per-centages, we have :—

	÷ At. Wgts.	÷ N = 1.
C = 48·18	4·015	2·7
H = 6·53	6·530	4·3
N = 20·92	1·494	1·0
O = 24·37	1·523	1·0
	= C_3H_4NO.	

2.—Water Extracts of Human Brains.

The water extracts were precipitated with excess of gold chloride, and the precipitate thus obtained was decomposed by hydrothion. On concentration of the resulting filtrate a crop of crystals was deposited. These crystals proved to consist of *hypoxanthine*, and its silver nitrate compound was prepared, re-crystallised from water strongly acidulated with H N O_3, and identified.

The mother liquor after the above crystals were separated was passed through the phospho-molybdic acid process and the excess of baryum removed by C O_2. From the solution the gold salt was reconstructed, and an attempt was made to obtain it as hydrochlorate in a crystalline form, but concentration was fatal to the project.

The mother liquor of the Au Cl_3 precipitate was freed from excess of gold by S H_2 and extracted during a long period with large volumes of ether. These ether extracts on distillation left a residue which furnished a crystalline zinc salt and a mother liquor, the bodies being probably identical with those prepared in a similar way from ox brain water extract (lactate of zinc and glycerin ?).

Continued extraction with ether gave rise to the formation in the solutions of crystals which were probably of the same nature as those described in the case of ox brains.

The mother liquors which remained after the Au Cl_3 and ether treatment were freed from sulphuric and phosphoric acids, and while alkaline precipitated by basic lead acetate. This precipitate was washed and decomposed by S H_2. Inosite was not sought for on account of the presence of much hydro-chloric acid introduced by the gold process. It was therefore neutralised by Mg O, and the concentrated liquid precipitated by alcohol.

Examination of this precipitate.—It was redissolved in water and re-precipitated by alcohol several times, by which means the excess of

$Mg\ Cl_2$ was removed in the mother liquors. The matter was then once more dissolved in water and precipitated while boiling with boiling solution of $Fe_2\ Cl_6$. This was done because the precipitate was only constant under these conditions, and was soluble in excess either of the solution or of the precipitate. The gelatinous precipitate, which became sandy on heating, was isolated, washed, dissolved in $N\ H_3$, and the iron removed by means of $S\ H_2$. The filtrate failed to crystallise on concentration. It gave the following reactions :—

(1.) Red in colour, acid to test paper.
(2.) With cupric acetate, slight greenish precipitate.
(3.) With $Fe_2\ Cl_6$, greenish brown precipitate soluble in excess.
(4.) $Hg\ Cl_2$, white precipitate.
(5.) $Cd\ Cl_2$ in alcohol, viscid precipitate soluble in water.
(6.) $Pb\ (C\ H_3\ O_2)_2$, thick white precipitate.
(7.) $Ag\ N\ O_3$, precipitate soluble in $H\ N\ O_3$ in the warm, and soluble in $N\ H_3$; decomposed on heating gently, becoming first of a carmine colour, then black.

The whole was now converted into silver salt, which blackened somewhat during washing and preparation for analysis. Dried at 100°.

(*a.*) 0·377 grm. gave 0·281 grm. Ag = 74·53 °/₀ Ag.

(*b.*) 1·1312 grm. gave 0·3774 grm. $C\ O_2$ and 0·120 grm. $H_2\ O$ = 1·178 °/₀ H and 9·105 °/₀ C.

Computation of analyses :—

Per-centages found.	÷ At. Wgts.	÷ Ag. = 1.
C = 9·105	0·758	1·09
H = 1·178	1·178	1·70
Ag=74·535	0·690	1·0
O =15·182	0·948	1·3

$= \times 3 = C_3\ H_5\ Ag_3\ O_4$.

74·535 °/₀ Ag leads to an atomic weight for the organic matter when multiplied by 3 of 108; $C_3\ H_8\ O_4 = 108$. This salt therefore is the fully saturated silver salt of a tribasic acid isomeric with glyceric.

The products then obtained in this study were—
Hypoxanthine.
A second base not analysed.
Lactic acid.
New tribasic acid.
Perhaps glycerine.

IV.—ANALYTICAL TECHNICAL INQUIRIES.

1.—Note on the Specific Gravity of Human and Bovine Brains, and their White and Grey Matter, and on the Determination of the Relative Amounts of White and Grey Matter.

The present statement is a preliminary notice of some experiments which have led to the solution of an anatomical problem hitherto believed to be unattainable, and to some remarkable pathological data.

The specific gravity of the white and grey matter differs within limits, which are much wider in disease than in health ; but in all cases grey

matter is of a lesser specific gravity, or more watery, than white matter, which is denser, or less watery.

Given the weight in air of an entire brain, and given the specific gravity of the entire brain, and given the specific gravities of the grey and the white matter respectively of the same brain, a simple calculation must lead us to the quantities of white and grey matter composing this brain.

It was easy enough to determine the specific gravities of portions of grey and white matter. But the determination of the specific gravity of an entire human brain required the construction of a new apparatus. This has just been completed, and will be employed as materials may be obtained.

I hope that this method of inquiry may help to throw light on brain diseases which are commonly the causes of various forms of madness. In a case of sclerosis the density of the white matter was actually found increased, as the anatomical term implies, its specific gravity being 1049. *But the grey matter was not only not higher in its specific gravity, but was actually below the normal specific gravity commonly assigned to grey matter* in physiological text books, namely as low as 1028.

A few determinations of the specific gravity of some entire ox brains led to 1034 and 1035 as average resultants.

2.—Note of an Essay on Combustion in Vacuo.

This paper was read before the Chemical Society, and published in their Journal (Vol. 2, 1876,) under the title "*Note of some Trials of Frankland and Armstrong's Combustion Process.*" *By J. L. W. Thudichum and C. T. Kingzett.* The authors show that this process is applicable to investigations in physiological chemistry, where the quantities of matter at the command of the investigator are often so small as not to admit of complete analyses by the ordinary methods.

In this method of analysis the determination of the nitrogen and carbon in organic substances, and of the relation of the one element to the other, can be conducted on a few centigrams of material, if the oxide of copper which is employed be free from occluded carbon. For this purpose it must be prepared as directed by Frankland and Armstrong, or must, as shown by the authors of the present essay, be heated to bright red heat in vacuo before use. But even should this not be done, and oxide of copper as ordinarily employed be used, the nitrogen determination is thoroughly trustworthy. Further, this method is available for determination of the nitrogen contained in all ammonium salts ; thus, in the case of nitrate of ammonium both the nitrogen of the nitric acid and of the ammonium is set free, and the amount obtained exactly corresponds with that required by theory.

3.—Note of an Essay on the Determination of Hydrogen occluded by Copper.

This paper was read before the Chemical Society, and published in their Journal (Vol. 2, 1876,) under the title "*On the Determination of Hydrogen occluded by Copper, with special reference to Organic Analyses.*" *By J. L. W. Thudichum and Henry W. Hake.*

It had been advanced that an error of excess in hydrogen determinations (in combustion of organic bodies with cupric oxide and metallic copper) was introduced by the use of the metallic copper, which substance, after the usual preparatory process of oxidation at a red heat in air and subsequent reduction at a red heat and cooling in an atmosphere of hydrogen, occluded a considerable quantity of this gas ; that indeed a

source of error existed in material used for the purpose of ensuring the utmost accuracy. To avoid the error the use of silver wire gauze had even been recommended. An examination of previous quantitative experiments made with regard to the occlusion of hydrogen by copper by Melsens, Graham, and Johnson, showed that the results arrived at had no concatenation whatever, a fact only to be explained by the varying conditions under which the respective experiments were made.

Experiments were therefore instituted in the Pathological Laboratory to determine the extent and conditions of occlusion of hydrogen by the ordinary copper wire gauze used in combustions. The amount occluded in each experiment was determined by exhausting at a red heat a tube containing the wire gauze rolls, after these had been subjected to the above-mentioned oxidation and reduction and cooling in hydrogen, and the gas so obtained collected over mercury and measured.

The results arrived at are of analytical importance, and are as follows :—

(1.) That the amount of hydrogen occluded by copper wire gauze which has undergone the usual process of oxidation and reduction *more than once*, is so small as to cause the inappreciable error of about 0·0039 per cent. excess of hydrogen, on the assumption that 0·4 grm. substance is employed for analysis.

(2.) That the amount occluded by copper wire gauze which has not been previously subjected to this process is also extremely small, and might also, except in the most accurate determinations, be disregarded, causing an error only of about 0·025 per cent. excess of hydrogen.

(3.) That all possible error due to occlusion of hydrogen by copper wire gauze may be entirely avoided by a very simple expedient, viz., by allowing the copper after reduction at a red heat in an atmosphere of hydrogen to cool in an atmosphere of carbonic anhydride.

It gives me great pleasure to record the ability, skill, and assiduity with which, in the course of these inquiries, I have been aided by my assistants, Messrs. C. T. Kingzett and H. W. Hake, Ph.D.

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